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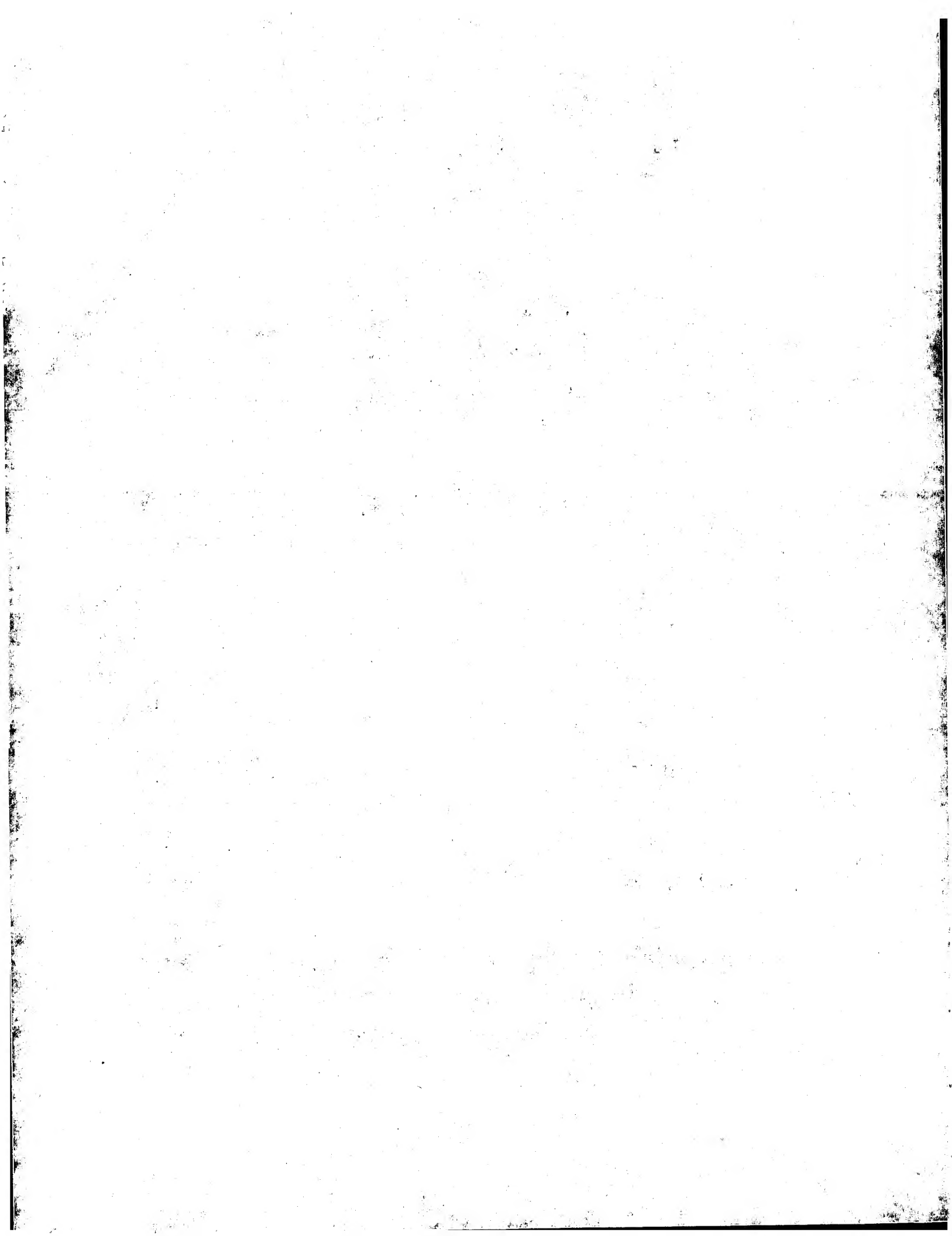
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US94/00222 <b>(22) International Filing Date:</b> 5 January 1994 (05.01.94) <b>(71) Applicant (for all designated States except US):</b> ARQULE, INC. [US/US]; Suite 3600, 200 Boston Avenue, Medford, MA 02155 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> HOGAN, Joseph, C., Jr. [US/US]; 50 Oak Avenue, Belmont, MA 02178 (US). <b>(74) Agents:</b> FANUCCI, Allan, A. et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHOD OF MAKING POLYMERS HAVING SPECIFIC PROPERTIES  <b>(57) Abstract</b>  A method of making a polymer having specific physiochemical properties by forming a first module having a structure which includes at least two structural diversity elements suitable to impart a desired physical property to a polymer which is made from said monomer; and reacting one or more modules to form a polymer having specific physiochemical properties. The base module can be formed by reacting a first compound having at least one structural diversity element and a first reactive group, with a second compound having at least one structural diversity element and a second reactive group, wherein the first and second groups combine by an addition reaction. Specifically, an aminimide compound, an oxazolone compound or derivatives thereof are useful as base modules in the invention.		

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## METHOD OF MAKING POLYMERS HAVING SPECIFIC PROPERTIES

### FIELD OF THE INVENTION

5       The present invention relates to a novel method of controlled polymerization to produce encoded synthetic polymers, involving the stepwise assembly of discrete modules having selected structural features in a manner so as to produce a polymer having (1) a precisely ordered sequence of structural  
10       units; or (2) a precisely ordered sequence of structural units and a specific uniform chain length and molecular weight, depending on the particular strategy chosen; and (3) resultant physiochemical and biological properties which are the sum of the individual properties of the modules and their specific  
15       arrangement in the polymer.

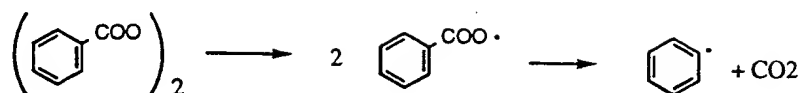
### BACKGROUND OF THE INVENTION

20       Existing polymerization methods fall into one of two basic types; (1) Addition or Chain Growth Polymerization; and (2) Condensation or Step-Growth Polymerization.

Chain growth polymerizations most commonly utilize monomers possessing reactive carbon-carbon double bonds, although other species, such as cyclic ethers, e.g., ethylene and  
25       propylene oxide and aldehydes, e.g., formaldehyde, can be polymerized in this way. These chain-growth polymerizations are characterized by the fact that the free radical, ionic or metal complex intermediates involved in the process are transient and can not be isolated. A generalized example for a simple free  
30       radical initiated vinyl polymerization is shown below:

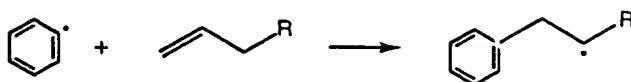
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## 1. Formation of initiator



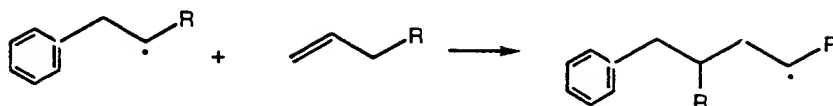
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## 2. Initiation

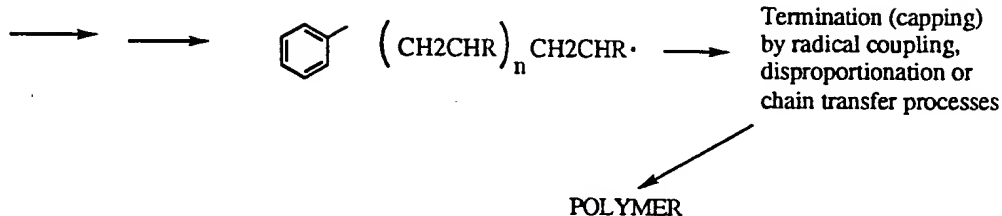


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## 3. Propagation



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Step-growth polymerizations involve reactions which occur between molecules containing multiple reactive groups which can react with each other. An example of this is the well-known reaction of a glycol and a dibasic aromatic acid to give a polyester.

It can be readily seen that the use of multiple reactive monomers possessing groups with similar or equivalent reactivities with this method produces a mixture of individual polymer species having random arrangements of monomeric sequences and only statistical control of the resulting stoichiometric make-up.

While many different variations of these two classes of polymerization reaction schemes exist, e.g. initiation may be cationic, radical, anionic, sequential aldol, ring-opening or displacement, and many different reactive species may be employed, e.g. electron deficient alkenes, epoxides, polyamines,

35

hydroxyesters, etc., all of these variations possess a common limiting feature - they all rely on a statistical or average stoichiometric control of the final polymeric product. This is achieved through the careful selection and control of the reaction conditions, such a concentration of monomers, agitation conditions, catalyst level, time/temperature cycles, etc.. These existing polymerization methods do not have any ability to control the exact constitution or length of any specific individual polymer chain. The properties of the polymers produced via these processes are, in fact, a statistical average of the properties of a complex mixture of subtly differing individual polymer species having a range of molecular weights and containing differing combinations and sequences of monomers along the chains. Even in the simplest example of a step growth polymerization involving only two reactants, where the product is a polymer containing a single repeating structural motif, the product obtained will consist of a statistical mixture of a large number of individual molecules each having differing lengths and molecular weights.

In spite of these limitations, those skilled in the art have developed strategies by which these methods can be exploited. Average chain length can be controlled roughly by the ratio of initiator to monomer, or by quenching with an additive giving a range of molecular weights. Macroscopic properties can be modulated by the addition of comonomers which are incorporated randomly into the backbone. However, these methods possess no ability to have discreet or even reproducible microsequence control, and the "address" of a singular functionality added to the polymerization reaction is statistically determined.

Most natural biological polymers, such as oligonucleotides, proteins and polysaccharides, on the other hand, contain precise sequences of monomer units which confer the polymer with highly specific functional properties, including a specific three dimensional structure. Recent advances in the understanding of the complex mechanisms of biochemical processes and of the underlying structure-function relationships of biological

polymers involved in the replication (DNA-DNA), storage (DNA), transcription (DNA-RNA), translation (RNA-protein), communication, recognition, control (proteins, peptides, carbohydrates) and function (proteins, oligosaccharides) of all  
5 biological systems have illuminated the exquisite sensitivity of these polymers to microsequence variations. A classic example of this is sickle cell anemia which has been shown to be due to a single point mutation in the genetic sequence encoding for the beta chain of hemoglobin. As a result of this mutation, the  
10 abnormal hemoglobin contains a single valine in place of a glutamine in the sequence of the protein. This results in an abnormal shape for the hemoglobin, producing the characteristic sickle-shaped cells and the resulting tragic pathological consequences .

15 The biosynthesis of these biopolymers can be viewed, at a molecular level, to consist of a highly organized series of individual catenation steps, each carried out with specific reactants under highly controlled conditions and mediated by biocatalytic agents, principally enzymes. All of the monomers  
20 necessary for the construction of these biological polymers are present in the vicinity of the reaction area and are carried by chaperone molecules to the site of their incorporation into the growing chain, where they are released and coupled. Since these polymers were designed by nature to carry out their highly  
25 specific functions under physiological conditions (water at pH 7 and physiological temperatures, etc.), and have been programmed by nature to be subject to natural biochemical transformations, such as proteolytic decomposition, they are usually not robust (notable exceptions include structural  
30 polymers such as chitin, cotton, skin, silk, hair and other structural materials ) and are easily decomposed or denatured by exposure to non-physiological conditions, such as elevated temperatures, organic solvents, extremes of pH, etc.. As a result, these molecules are generally ill suited for tasks other than  
35 their proper biochemical ones.

Simply put, the makers of polymers, while being able to statistically achieve good and consistent macroscopic properties



in the polymeric materials which they produce, have not had any way, up to this point, to control the microscopic make-up of their product. Nature, in producing biomacromolecules, has evolved systems which allow exquisite control over both the  
5 microscopic make-up and the macro-structure of its functional polymers. However, these polymers are severely limited in the variety of uses to which they may be applied by their chemical constitution, their lack of stability towards chemical and  
10 biochemical agents and their sensitivity to changes in environmental conditions, such as temperature. In addition, the nature of natural scaffolds and substituents and their sensitivity to the chemical conditions necessary to manipulate and to transform them severely limits their utility in producing new  
15 materials from these components.

#### SUMMARY OF THE INVENTION

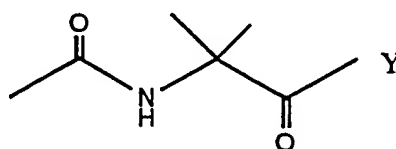
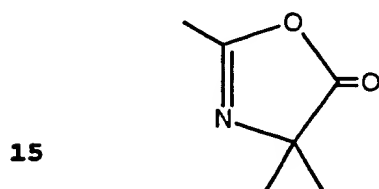
This invention relates to a method of making a polymer having specific physiochemical properties by forming a base  
20 module having a structure which includes at least two orthogonal reactivity or structural diversity elements suitable to impart a desired physiochemical property to a polymer which is made from said monomer; and reacting one or more modules to form a polymer having specific properties. The module is  
25 preferably an aminimide compound, an oxazolone-compound, or a derivative thereof. The module is prepared from first and second components which provide the orthogonal reactivity elements. The module may contain 2, 3, 4 or more orthogonal  
30 reactivity elements, depending on the desired performance properties of the resultant polymer.

The polymer chains are started with a terminus or starter module containing a single reactivity element and are capped at the desired point in the synthesis with a second terminus or  
35 capping module containing a single reactivity element in order to control the length of the chain.

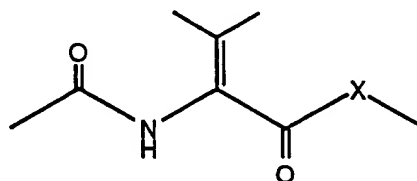
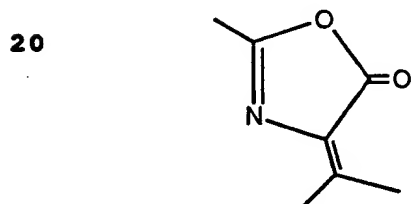
The base module can be formed by reacting a first compound having at least one structural diversity element and a

first reactive group, with a second compound having at least one structural diversity element and a second reactive group, wherein the first and second groups combine by an addition reaction.

- 5 Preferably, the first compound is produced by forming an oxazolone compound having at least one structural diversity element attached thereto and reacting it with a nucleophile or carbonyl compound which contains at least one structural diversity element to form a base module having one of the  
10 following structures:



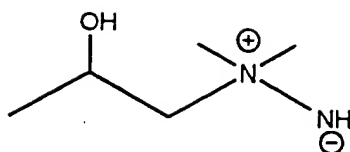
and



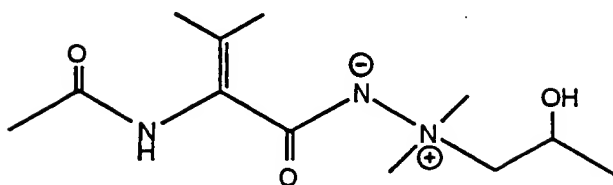
- 25 wherein at least two of the unconnected lines are connected to structural diversity elements.

- Alternatively, it is also preferred to provide the first compound as an aminimide-forming compound having at least one structural diversity element attached thereto and to react it  
30 with an oxazolone or an oxirane compound, which contains at least one structural diversity element to form a base module having one of the following structures:

35



5



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wherein at least two of the unconnected lines are connected to structural diversity elements.

15 In particular, this method can be used to make polymers having a designed water solubility. This invention still further relates to the polymers produced according to these methods. Still further, this invention relates to uniform polymers comprising a multitude of long chain molecules each of which  
20 have the same molecular weight and the same length.

This ability to produce polymeric chains of specific sequence and composition has great utility in the fabrication of a new generation of functional oligomeric and polymeric materials for a wide spectrum of applications, such as drugs, chiral  
25 recognition elements, catalysts, separations tools, biomaterials, fibers, plastics, membranes, beads and gels.

### DETAILED DESCRIPTION OF THE INVENTION

30 The present invention discloses a fundamentally new approach to the fabrication of oligomeric and polymeric molecules involving (1) the use of modular units which can contain at least two orthogonally reactive elements and are capable of bearing a wide variety of structural information, such  
35 as specific geometry, functionality, substituents, etc. (2) the stepwise assembly of polymers from these modules (a) by carrying out catenation or coupling reactions one step at a time or (b) by constructing "sub assemblies" of modular units one

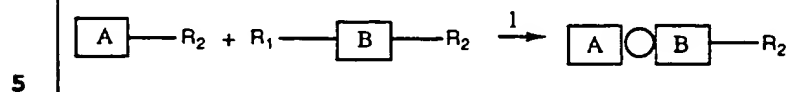
step at a time and connecting them together in a concerted manner in such a way that the resulting polymer has a controlled (encoded) microsequence and a resultant overall functional activity, which is the sum of the functional activities of the constituent modular parts. This approach involves the design and construction of a scaffolding superstructure which sets the basic spacing and geometry of the molecule and serves to arrange and orient the attached substituent groups in a manner suitable to achieve the desired functional property and, simultaneously, serves to allow the incorporation of desired pendant substituents in the appropriate positions having the appropriate desired relationships to each other and to the scaffold to produce the desired functional effect in the final polymer.

In this application, the term "polymer" is used to refer to any catenated structure containing a sufficient number of modules to carry enough structural information to impart the desired property to the resulting polymer, usually consisting of a minimum of three monomers plus two terminus (starter and capping) modules.

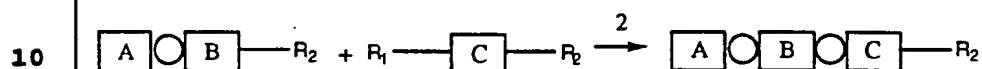
A key element of this method is the presence of at least two orthogonal reactivity elements in the modules. Orthogonal reactivity elements are defined as those elements which are either (A) multiple reactive groups which are capable of being "turned on" independently of each other or (B) multiple differing reactive states which may be addressed or brought into being at different times or under different conditions in the catenation sequence. It is highly desirable, although not absolutely necessary, that the individual reactions be high-yielding addition reactions with no by-products, so that isolation and purification steps are not necessary between cycles. The two basic schemes are illustrated below:

A. Multiple Reactive Groups

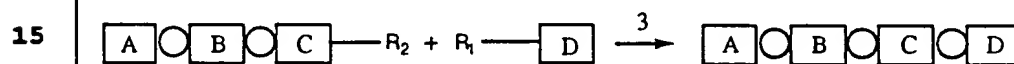
Step 1. Coupling of "Starter Module" with "Extender Module"



Step 2. Coupling of "Extender Module" with Chain



Step 3. Coupling of "Capping Module" with Chain



20 Where R1 and R2 = groups capable of undergoing addition reactions with each other, and A, B, C, D are either monomeric modules or "sub assemblies" containing multiple modules stitched together in a sequence specific manner.

25

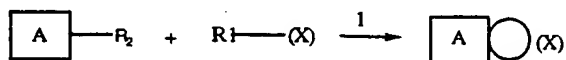
30 B. Multiple Reactive States

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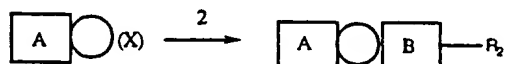
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Step 1. Coupling of "Starter Module" with "Extender Intermediate"

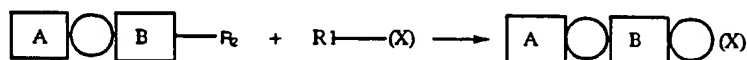


Step 2. Transformation of Terminal Intermediate Group to Reactive Group Bearing Module



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Step 3. Coupling of "Extender Intermediate" with Chain



15

Step 4. Transformation of Terminal Intermediate Group to Reactive Group Bearing Module



20

Step 5. Coupling of "Capping Module" with Chain



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Where R1 and R2 are groups capable of undergoing addition reactions with each other, and A, B, C, D are either monomeric modules or "sub assemblies" containing multiple modules stitched together in a sequence specific manner.

30

These reactive orthogonalities allow each discrete addition reaction to be carried to completion before the next individual addition reaction is undertaken. If desired, the intermediate products may be isolated following each individual step. In this critical respect this method is fundamentally different from both chain and step-growth polymerization methods.

35

In addition to the stepwise sequential construction of polymers one unit at a time as illustrated, this method may be utilized to construct oligomeric "sub assemblies" having designed microsequences, and properties. These may then be connected

together in a separate step to produce higher order assemblies, which may themselves again be connected together to, ultimately form a polymer having the desired set of properties. This strategy requires that one of the orthogonal reactivity  
5 elements on each sub-unit be either protected with an appropriate removable blocking group or contain a third orthogonally reactive group. These reactions may be carried out with modules containing > 2 orthogonally reactive elements to  
10 produce three dimensionally cross linked networks and structures. Alternatively these sub assemblies may be combined with appropriately functionalized "classical" modules to produce hybrid polymers.

A new approach to the stepwise sequential  
15 construction of novel oligomeric and polymeric molecules is described. This approach involves the development of a process whereby molecular building blocks which contain appropriate atoms and functional groups and posses at least two  
20 orthogonally reactive elements are connected together in a stepwise sequential fashion to allow the modular assembly of oligomers and polymers with tailored properties; each module  
-contributing to the overall properties of the assembled molecule. This approach to molecular construction is applicable to the  
25 synthesis of all types of molecules, including but not limited to mimetics of peptides, proteins, oligonucleotides, oligosaccharides, classical polymers, variants, hybrids of these and to fabricated structures and materials useful in materials science. It is  
analogous to the modular construction of a mechanical device  
30 that performs a specific operation wherein each module performs a specific task contributing to the overall operation of the device.

Examples of suitable modules containing appropriate orthogonally reactive elements for utilization in this method are  
35 given below:

Several of the specific modular chemistries chosen to illustrate and exemplify the invention are capable of bearing and maintaining chiral centers throughout the various steps

involved. Where this is the case, the chirality will be shown. This is not intended to limit the scope of the invention to chiral materials, since there are a large number of variations and applications where structural stereocontrol is not required or  
5 where achiral materials are employed

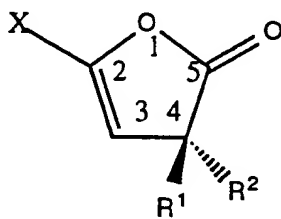
## POLYMERS PRODUCED FROM OXAZOLONES

### Oxazolone Modules

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A type of oxazolone module appropriate for use in the present invention may be represented by the following general structure:

15



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where R & R' are the same or different and X represents either a group having orthogonal reactivity to the oxazolone ring or a structural moiety, depending on which of two possible assembly  
25 strategies is chosen, as outlined below. R<sup>1</sup> and R<sup>2</sup> differ from one another and taken alone each signifies one of the following: alkyl including cycloalkyl and substituted forms thereof; aryl, aralkyl, alkaryl, and substituted or heterocyclic versions thereof; preferred forms of R1 and R2 are the side chain substituents  
30 occurring in native polypeptides, oligonucleotides, variants or mimetics of these, carbohydrates, pharmacophores, variants or mimetics of these, or any other side chain substituent which can be attached to a scaffold or a backbone to produce a desired interaction with a target system.

35

The substituents R & R' may be of a subset of hydrophilic substituents such as, but not limited to hydroxymethyl,



hydroxyethyl, hydroxypropyl, thioethyl, thiomethyl; carboxymethyl, carboxyethyl, ethylcarboxamido, methylcarboxamido; aminomethyl, aminoethyl, aminopropyl, guanidinypropyl, guanidinylbutyl; mono-, di-, and  
5 triaminobenzyl, mono-, di-, and trinitrobenzyl; mono-, di-, tri-, and tetrahydroxy benzyl, mono- or polyhydroxyaryl (e.g. pyrogallol); heteroaryl (e.g. alkylpyridines, imidazole, alkyltryptophans); alkyl nucleotides; all substituted  
10 pyrimidylalkyl and substituted purinealkyl moieties; mono-, di-, and oligosaccharide (e.g. N-methylfucosamine, maltose and the calicheamicin recognition sequence respectively); alkylsulfonates, alkylphosphonates; a-polyfluoroketones; secondary, tertiary and quaternaryamines; hydrazines and the hydrazinium salts. R and R' may also come from the subset  
15 consisting of hydrophobic substituents such as, but not limited to: hydrogen; methyl, ethyl propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, iso-, sec-, and neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.; vinyl, propenyl, butenyl or other alkenyl groups; acetylenic side chains; aromatic polycyclics (e. g. biphenyl, binaphthyl, naphthylphenyl, phenylnaphthyl); fused  
20 aromatic polycyclics (e.g. anthracene, phenylene, pyrene, acenaphthene, azulenes); fused polycyclics (e. g. decalin, hydrindanes, steroids); phenyl, alkylphenyl, phenylalkyl; benzyl, mono-, di-, tri-, and tetraalkylbenzyl; mono-, di-, and  
25 trialkoxybenzyl; heteroaryl (e.g. furyl, xanthanyl, quinolyl); methoxyalkyl, ethoxyalkyl, aryloxy; methylmercaptans, ethylmercaptans, alkyl thioethers and arylthioethers; dyes and fluorescent tags (such as rhodamine or fluorescein); alkyl esters, aryl esters, aralkyl esters, and alkylaryl esters.  
30

### Polymerization Strategies

These oxazolone modules may be employed to construct  
35 oligomers and polymers in two different ways:

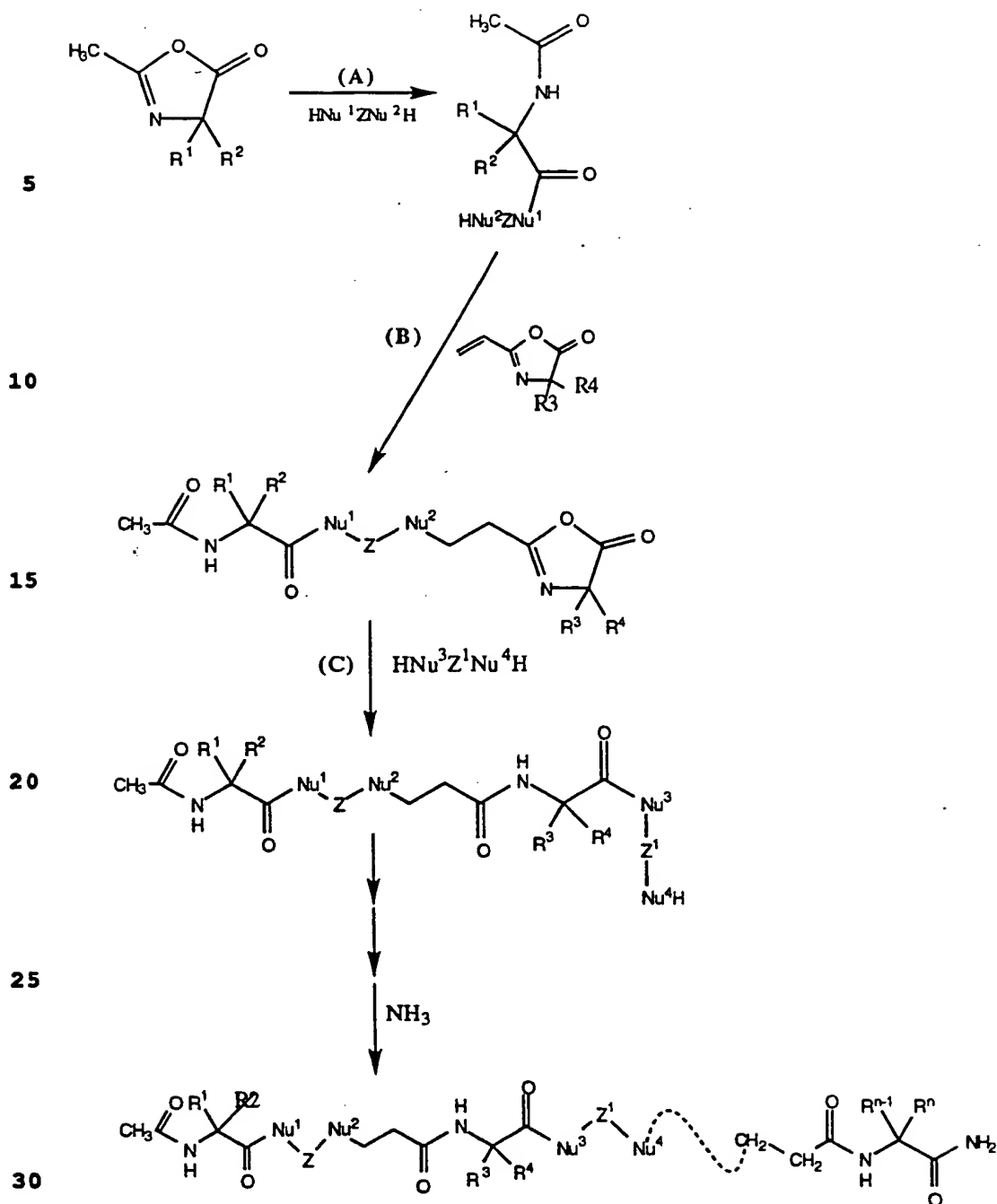
#### A. Ring Opening Reaction/2-Position Substituent Addition-

Oxazolones with suitable substituents at the 2-position (X = an orthogonally reactive group) may act as orthogonally reactive agents suitable for the construction of the polymers which are the subject of the present invention. This  
5 may be accomplished by carrying out alternating ring opening and 2-position substituent addition reactions with suitable bifunctionally reactive species. One terminus of these reactive elements should contain an SH, OH or NH group capable of  
10 undergoing ring-opening addition reaction with the oxazolone ring. The second terminus of the reactive element should contain a group capable of undergoing addition reaction with X. The choice of this second group, obviously, depends on the nature of the specific X group chosen in each case. Appropriate 2-position  
15 substituents include vinyl groups, which make the oxazolone a Michael acceptor, haloalkyl and alkyl sulfonate esters and epoxide groups. This is shown below for the case of alternating ring opening and Michael additions to the double bond of a 4,4-disubstituted-2-vinyloxazolone by appropriate dinucleophilic  
20 species produces polymeric chains, as shown

25

30

35



In the above sequence of reactions,  $\text{HNu}^1\text{-Z-Nu}^2\text{H}$  represents a structure containing two differentially reactive nucleophilic groups, such as methylamino-ethylamine, 1-amino propane-3-thiol, and so on; groups  $\text{Nu}^1$ ,  $\text{Nu}^2$ ,  $\text{Nu}^3$  and  $\text{Nu}^4$  need not be identical and  $\text{Z}$  is a generalized structural group connecting  $\text{HNu}^1$  and  $\text{HNu}^2$ .  $\text{HNu}^1\text{-Z-Nu}^2\text{H}$  may contain two nucleophilic groups of

differential reactivity, as stated above, or if  $\text{Nu}^1$  and  $\text{Nu}^2$  are of comparable reactivity one of the nucleophilic groups is protected to prevent it from competing with the other and deprotected selectively following acylation; protecting groups commonly used  
5 in the art of peptide synthesis (e.g., for the nucleophilic groups such as amino, hydroxyl, thio, etc.) are useful in the protection of one of the Nu substituents of the structure  $\text{HNu}^1\text{-Z-Nu}^2\text{H}$ . The product of the acylation reaction with  $\text{HNu}^1\text{-Z-Nu}^2\text{H}$  (after Nu-deprotection, if necessary) is further reacted with a new  
10 oxazolone unit in a Michael fashion, and this addition is followed by ring opening acylation with an additional dinucleophile; repetition of this sequence of synthetic steps produces a growing polymeric molecule.

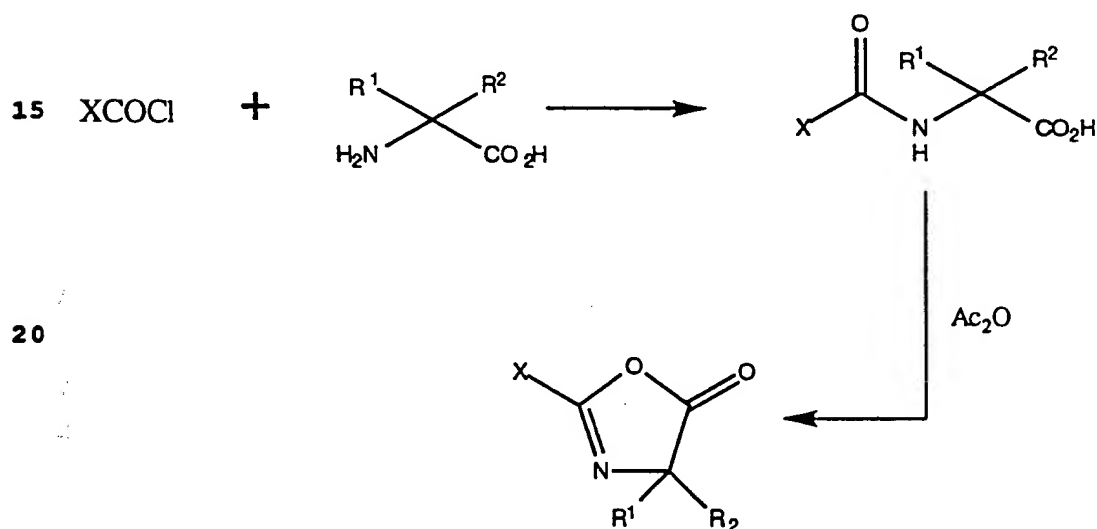
The Michael reaction step is usually carried out using  
15 stoichiometric amounts of nucleophile AXH and the oxazolone in a suitable solvent, such as toluene, ethyl acetate, dimethyl formamide, an alcohol, and the like. The selectivities of the Michael and oxazolone ring-opening processes impose certain  
20 limitations on the choice of the nucleophiles shown above. Specifically, nucleophiles of the form ROH tend to add primarily via the ring-opening reaction, and usually require acidic catalysts (e.g.,  $\text{BF}_3$ ); thus,  $\text{Nu}^2$  should not be OH. Likewise, primary amines tend to add only via ring-opening, and  
25  $\text{Nu}^2$  should therefore not be  $\text{NH}_2$ . Secondary amines readily add to the double bond under appropriate reaction conditions. Nucleophiles of the form RSH will exclusively add via ring-opening if the sulfhydryl group is ionized (i.e., if the basicity of the reaction mixture corresponds to  $\text{pH} > 9$ ); on the other hand,  
30 such nucleophiles will exclusively add via Michael reaction under non-ionizing (i.e., neutral or acidic) conditions. During the Michael addition, it is important to limit the presence of hydroxylic species in the reaction mixture (e.g., moisture) to avoid ring-opening side-reactions.

The ring-opening reactions can be carried out either  
35 in an organic solvent such as methylene chloride, ethyl acetate, dimethyl formamide (DMF) or in water at room or higher temperatures, in the presence or absence of acids, such as

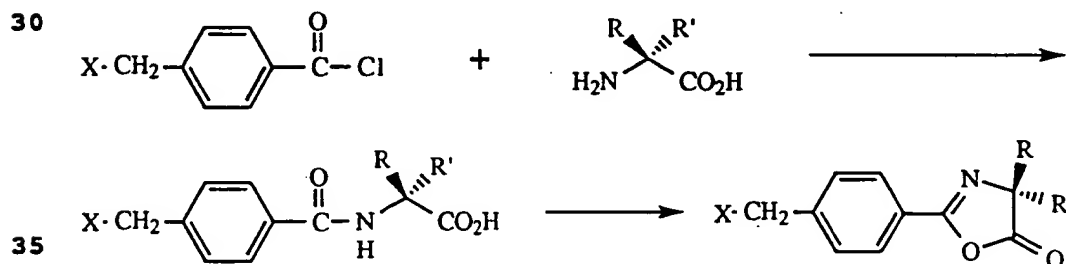
carboxylic, other proton or Lewis-acids, or bases, such as tertiary amines or hydroxides, serving as catalysts.

An example of the application of this strategy is given below for the synthesis of a subunit containing four structural modules and the subsequent assembly of these modules into a polymer containing repeating sequences of these specific subunits:

The required 4,4'-disubstituted oxazolone modules may be prepared from the appropriate N-acyl amino acid using any of a number of standard acylation and cyclization techniques well-known to those skilled in the art, e.g.:



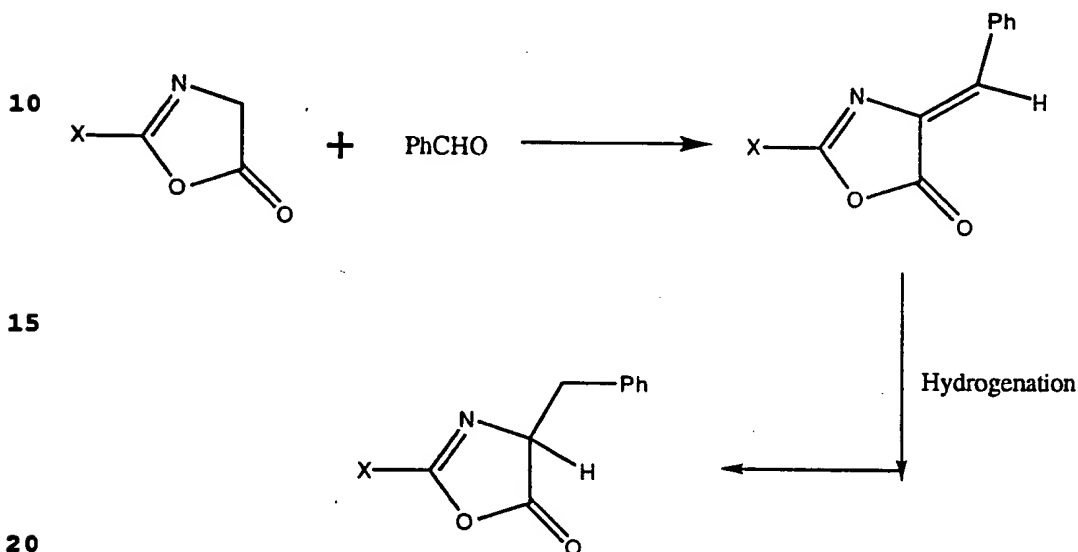
Alternative reactive groups may be introduced at the 2-position of the oxazolone in this way, as shown for a benzyl substituted reactive substituent:



A wide variety of 4-monosubstituted azlactones may be readily prepared by reduction of the corresponding

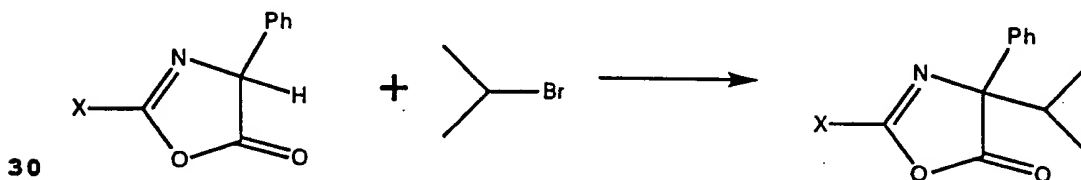
unsaturated derivatives obtained in high yield from the condensation reaction of aldehydes, ketones, or imines with the oxazolone formed from an N-acyl glycine (49 J. Org. Chem. 2502 (1984); 418 Synthesis Communications (1984))

5



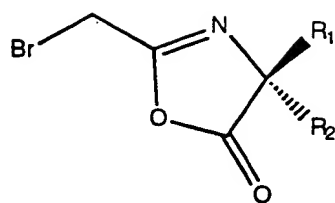
These may be converted to 4,4'-disubstituted oxazolones by alkylation of the 4-position, as in the following transformation (Synthesis Commun., Sept. 1984, at 763; 23

25 Tetrahedron Lett. 4259 (1982)):



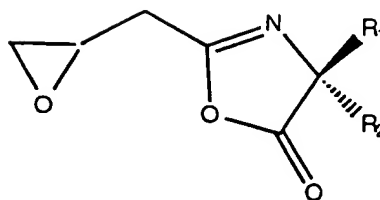
Other important bifunctionally reactive oxazolone derivatives which may be employed in these schemes include:

35



5

And



B. Alternating Sequences of Nucleophilic Oxazolidinone-Ring-Opening  
Addition Reactions Followed by Oxazolidinone-Forming Cyclization

10 Reactions

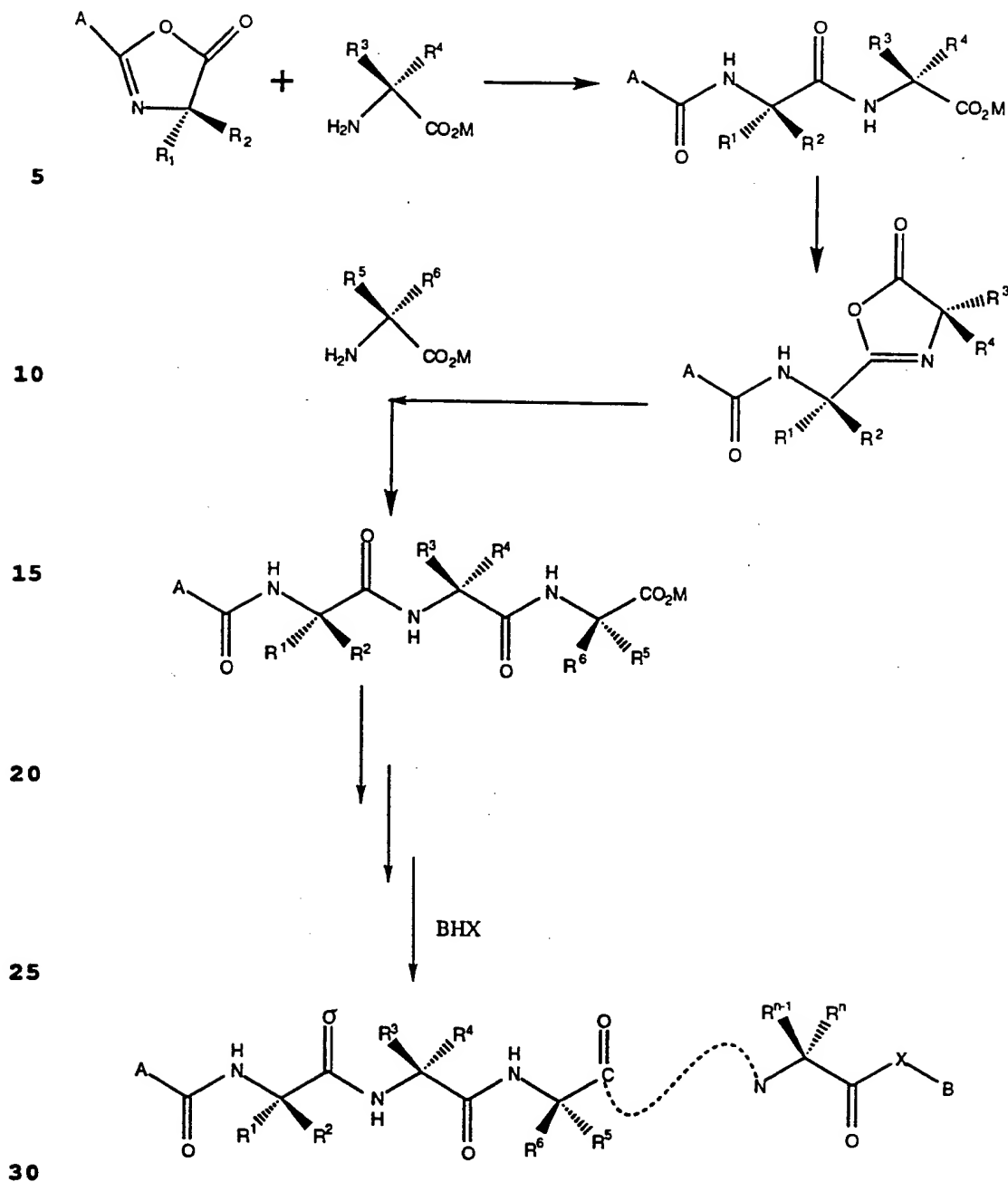
Alpha,Alpha'-Disubstituted Sequences

According to this approach, oxazolidinone modules are  
catenated via ring-opening nucleophilic attack by the amino  
15 group of an alpha,alpha'-disubstituted amino acid; the resulting  
adduct is subsequently cyclized to form a terminal oxazolidinone  
(with retention of chirality). This is then subjected to another  
nucleophilic ring-opening catenation reaction, producing a  
growing polymer as shown below. This procedure is repeated  
20 until the desired polymer is obtained.

25

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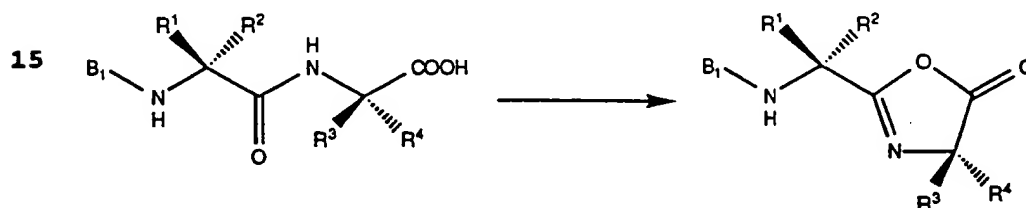


Wherein M is an alkali metal; each member of the  
 substituent pairs  $R^1$  and  $R^2$ ,  $R^3$  and  $R^4$ , and  $R^5$  and  $R^6$  differs  
 from the other and taken alone each signifies alkyl, cycloalkyl,  
 or substituted versions thereof, aryl, aralkyl or alkaryl, or  
 substituted and heterocyclic versions thereof; these substituent  
 pairs can also be joined into a carbocyclic or heterocyclic ring;

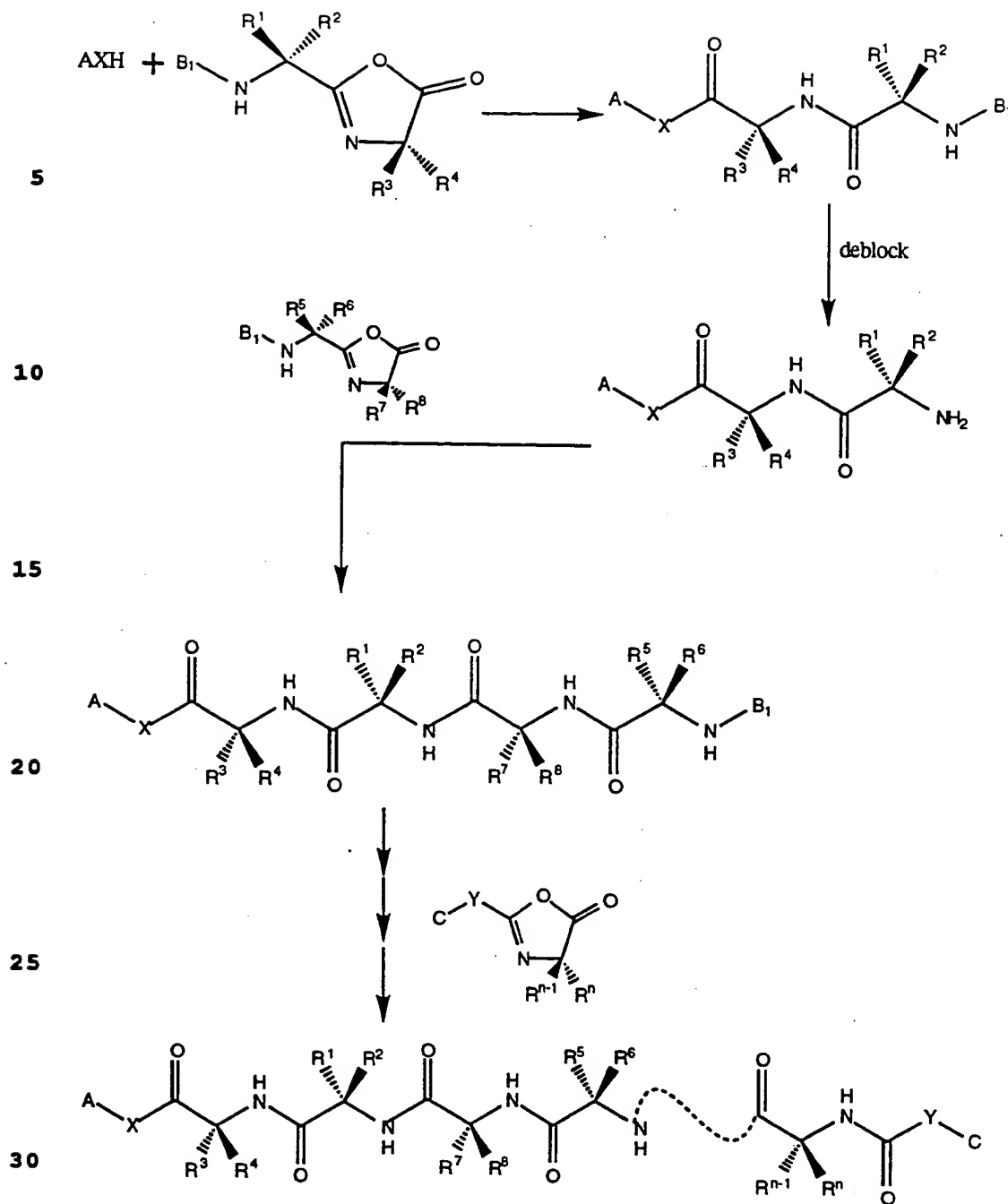


preferred forms of R1 and R2 are the side chain substituents occurring in native polypeptides, oligonucleotides, variants or mimetics of these, carbohydrates, pharmacophores, variants or mimetics of these, or any other side chain substituent which can be attached to a scaffold or a backbone to produce a desired interaction with a target system.; X represents an oxygen, sulfur, or nitrogen atom; and A and B are the substituents described above.

A chiral oxazolone derivative containing a blocked terminal amino group may be prepared from a blocked, disubstituted dipeptide, that was prepared by standard techniques known to those skilled in the art, as shown:



wherein B<sub>1</sub> is an appropriate protecting group, such as Boc (t-butoxycarbonyl) or Fmoc (fluorenylmethoxycarbonyl). One may then use this oxazolone to acylate an amine, hydroxyl, or sulfhydryl-group in a linker structure or functionalized solid support, represented generically by AXH, using the reaction conditions described above. This acylation is followed by deblocking, using standard amine deprotection techniques compatible with the overall structure of the amide (i.e., the amine protecting group is orthogonal with respect to any other protecting or functional groups that may be present in the molecule), and the resulting amino group is used for reaction with a new bifunctional oxazolone generating a growing chiral polymeric structure, as shown below:

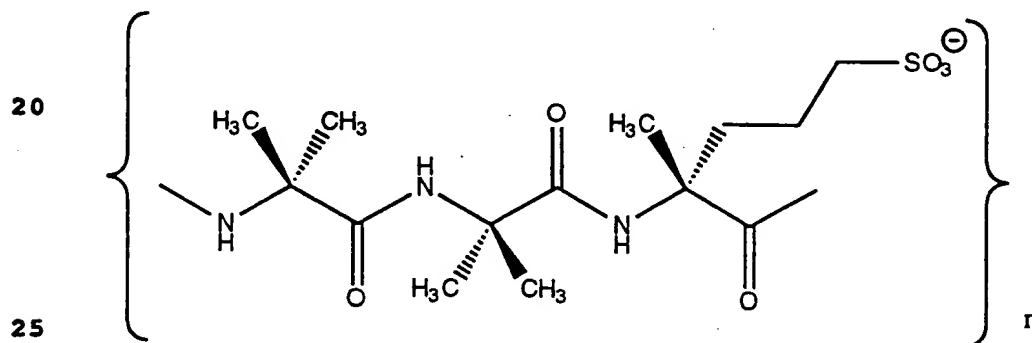


In the reaction shown above, Y is a linker  
 (preferably a functionalized alkyl group); X is a nitrogen of  
 suitable structure; an oxygen or a sulfur atom; each member of  
 the substituent pairs  $R^1$  and  $R^2$ ,  $R^3$  and  $R^4$ ,  $R^{n-1}$  and  $R^n$  differs  
 from the other and taken alone each signifies alkyl, cycloalkyl,

or functionalized versions thereof; aryl, aralkyl or alkaryl or functionalized including heterocyclic versions thereof (preferably, these R substituents mimic the side-chain of naturally occurring amino acids); substituent R can also be part  
 5 of a carbocyclic or heterocyclic ring; A is a substituent as described above; and C is a substituent selected from the set of structures for A; and B<sub>1</sub> is a blocking or protecting group.

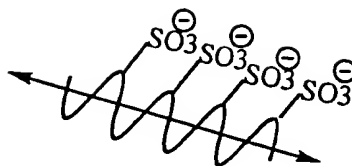
### Sub Assemblies

Alternatively, modular "sub assemblies" capable of conferring higher order structural properties may be pre-constructed and assembled together using these same reaction  
 15 sequences in a manner which allows control of the higher order structure. This is illustrated for the case of a polymer formed with a repeating pattern of alternating modules of the type::



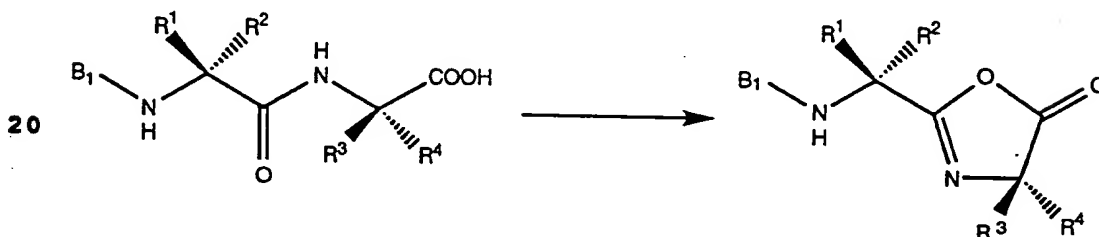
This polymer will form 3-10 helices, driven by the conformational restrictions imposed by the repetitive vicinal disubstitution. This triadic periodicity results in the formation of  
 30 a helical superstructure which has charged sulfonate groups lined up regularly along one side of the helix:

5

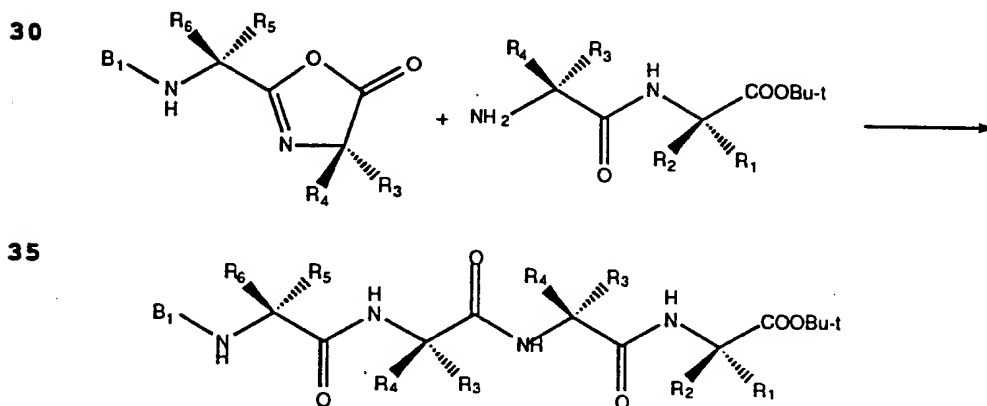


- 10 This "sub assembly" strategy may be used to generate higher order polymers in the following manner:

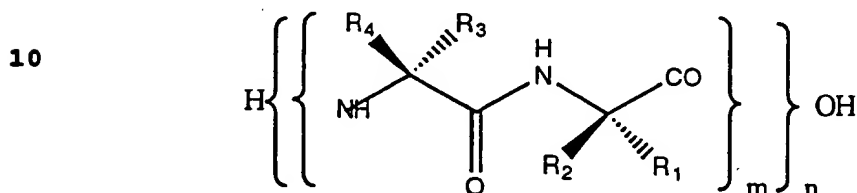
1. An oxazolone dimer containing a blocked terminal amino group may be prepared from a blocked disubstituted peptide,  
 15 prepared using standard techniques known to those skilled in the art, as shown:



- 25 2. This oxazolone may be coupled with a suitable c-terminal derivative of a second disubstituted dipeptide, as shown, to give the 4-mer module shown:



3. This process may then be repeated with the 4-mers to produce an 8-mer module; repeated again to form a 16-mer module, and so on, until a molecule having the desired length is obtained. At any point in this sequence, the protecting groups can be removed and the modules can be catenated together to form a polymer with repeating sequences of modules, as shown:

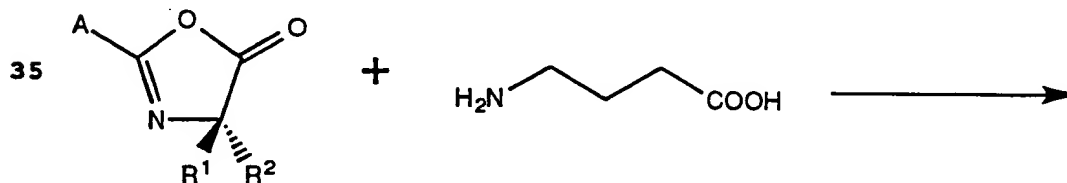


where m = number of iterative steps

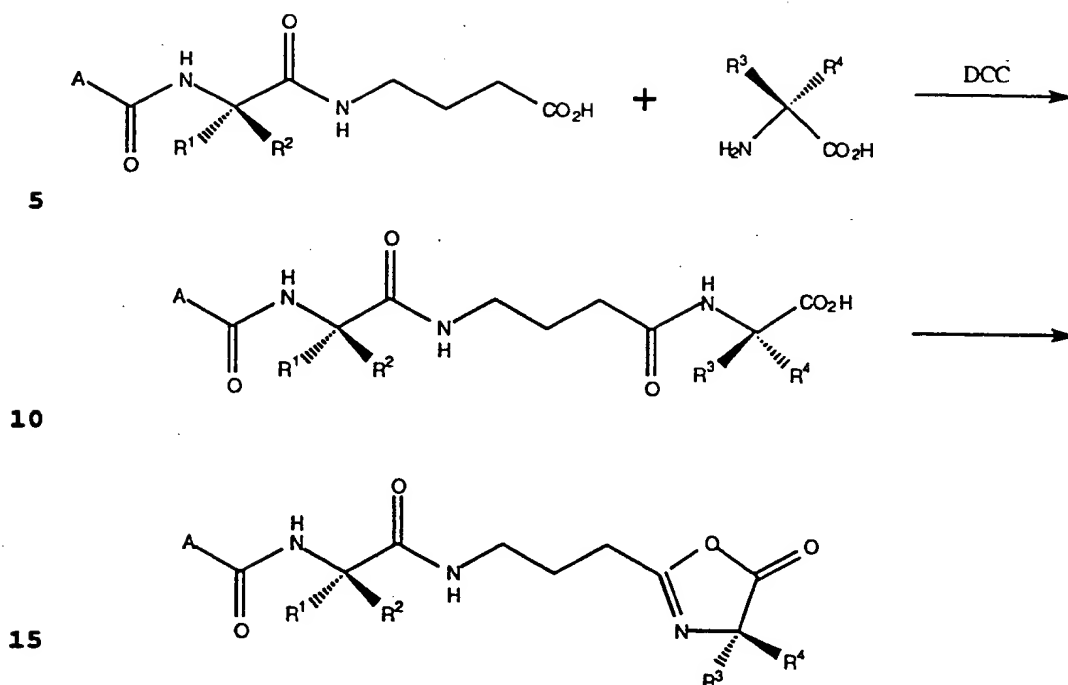
In cases where solubility problems are encountered as the size of the modules increases, the stability of the linkages allows the use of a broad array of standard or "exotic" reaction solvents, such as hexamethyl phosphoramidate. If necessary, solubilizing groups can be incorporated as side chain substituents or connecting modules.

#### Other Reactive Elements

At any point in the polymer syntheses shown above, a structural species, possessing (1) a terminal OH, -SH or -NH<sub>2</sub> group capable of ring-opening addition to the oxazolone and (2) another terminal group capable of reacting with the amino group of a chiral alpha, alpha'-disubstituted amino acid, may be inserted in the polymer backbone as shown below ;



SUBSTITUTE SHEET



This process may be repeated, if desired, at each step in the synthesis where an oxazolone ring is produced.

20 The bifunctional species used may be the same or different in the steps of the synthesis.

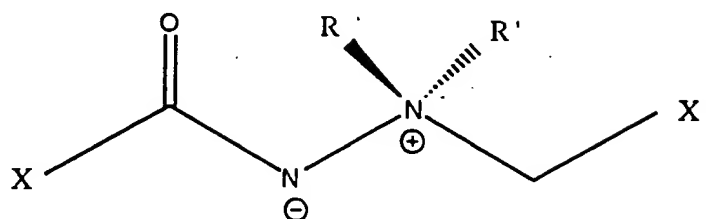
The experimental procedures described above for oxazolone formation and use of oxazolones as acylating agents are expected to be useful in the oxazolone-directed  
 25 catenations. Solubility and coupling problems that may arise in specific cases can be dealt with effectively by one with ordinary skill in the art of polypeptide and peptide mimetic synthesis. For example, special solvents such as dipolar aprotic solvents (e.g., dimethyl formamide, DMF, dimethyl sulfoxide, DMSO, N-  
 30 methyl pyrrolidone, etc.) and chaotropic (molecular aggregatebreaking) agents (e.g., urea) will be very useful as catenations produce progressively larger molecules.

### POLYMERS PRODUCED FROM AMINIMIDES

35

Stepwise sequential Reactions of 1,1-Disubstituted Hydrazines or Hydrazine Derivatives with Bifunctionally Reactive elements.

The aminimide monomer structure may be represented by the formula:



where R & R' are the same or different and X & X' are from the same groups as R or R' and/or represent the extension or remainder of a polymer chain..

The groups R & R' may be of a subset of hydrophilic substituents such as, but not limited to hydroxymethyl, hydroxyethyl, hydroxypropyl, thioethyl, thiomethyl; carboxymethyl, carboxyethyl, ethylcarboxamido, methylcarboxamido; aminomethyl, aminoethyl, aminopropyl, guanidinypropyl, guanidinybutyl; mono-, di-, and triaminobenzyl, mono-, di-, and trinitrobenzyl; mono-, di-, tri-, and tetrahydroxy benzyl, mono- or polyhydroxyaryl (e.g. pyrogallol); heteroaryl (e.g. alkylpyridines, imidazole, alkyltryptophans); alkyl nucleotides; all substituted pyrimidylalkyl and substituted purinealkyl moieties; mono-, di-, and oligosaccharide (e.g. N-methylfucosamine, maltose and the calicheamicin recognition sequence respectively); alkylsulfonates, alkylphosphonates; a-polyfluoroketones; secondary, tertiary and quaternaryamines; hydrazines and the hydrazinium salts. They may also come from the subset consisting of hydrophobic substituents such as, but not limited to hydrogen; methyl, ethyl propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, iso-, sec-, and neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.; vinyl, propenyl, butenyl or other alkenyl groups; acetylenic side chains; aromatic polycyclics (e. g. biphenyl, binaphthyl, naphthylphenyl, phenylnaphthyl); fused aromatic polycyclics(e.g. anthracene, phenylene, pyrene, acenaphthene, azulenes); fused polycyclics (e. g. decalin,

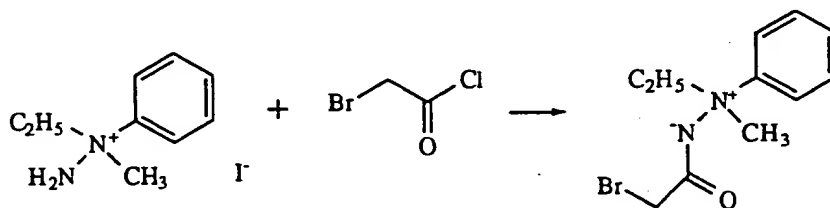
hydrindanes, steroids); phenyl, alkylphenyl, phenylalkyl; benzyl, mono-, di-, tri-, and tetraalkylbenzyl; mono-, di-, and trialkoxybenzyl; heteroaryl (e.g. furyl, xanthanyl, quinolyl); methoxyalkyl, ethoxyalkyl, aryloxy; methylmercaptans, ethylmercaptans, alkyl thioethers and arylthioethers; dyes and fluorescent tags (such as rhodamine or fluorescein); alkyl esters, aryl esters, aralkyl esters, and alkylaryl esters; polymeric support surfaces

### 10 Polymerization of Aminimide Subunits via Acylation/Alkylation Cycles

The following steps are involved in this synthesis:

1. Acylation of a hydrazinium salt with a molecule capable of functioning both as an acylating and as an alkylating agent producing an aminimide; BrCH<sub>2</sub>COCl and other bifunctional species, such as bromoalkyl isocyanates, 2-bromoalkyl oxazolones, etc., may be used as acylating agents under the reaction conditions given above.

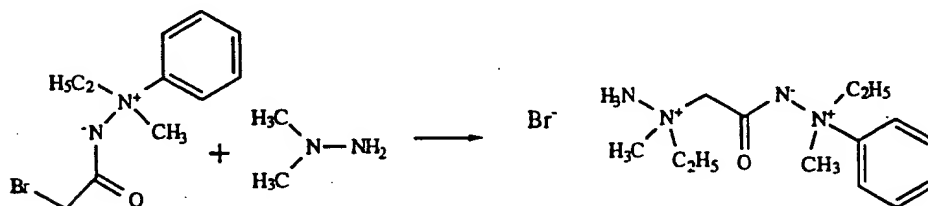
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2. Reaction of the product of the above reaction with a 1,1-disubstituted hydrazine to form an aminimide hydrazinium salt.

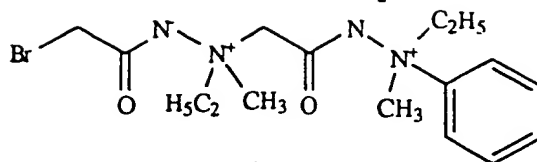
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35

3 Acylation of the product from step 2 with a bifunctional acyl derivative similar to those listed in step 1 above producing a dimer.





5

54 Repetition of steps 2 and 4 the required number of times to build the desired aminimide polymeric sequence.

6. Capping of the assembled sequence if desired, for example, by reaction with an acylating agent, such as acetyl chloride.

10

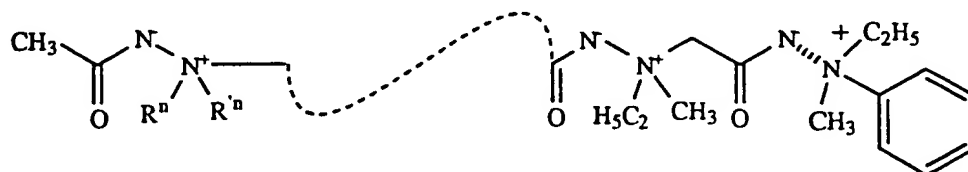
The experimental conditions (e.g. reaction-solvent, temperature and time, and purification procedures for products) for all of the above reactions were described above and are also well-known and practiced in the art. As the molecular weight of the products increases (e.g. in step 5 above) solubility and reaction-rate problems may develop if the reactions are run under the conditions that successfully gave products of much smaller molecular weight. As is well known from the art of peptide synthesis, this is probably due to conformational (folding) effects and to aggregation phenomena, and procedures found to work in the related peptide cases are expected to be very useful in the case of aminimide catenations. For example, reaction solvents such as DMF, or N-methyl pyrrolidone, and chaotropic (aggregate-breaking) agents, such as urea, are expected to be helpful in alleviating reactivity problems as the molecular-weight of the product increases.

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### Polymerization of Aminimide Subunits via Acylation/Alkylation Cycles

The following steps are involved in this synthesis;

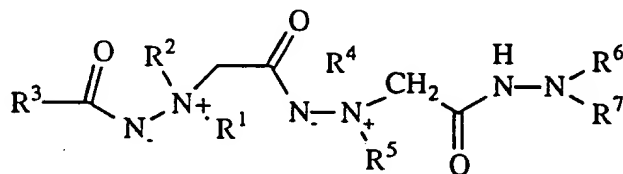
e.

1. Alkylation of an asymmetrically disubstituted hydrazide, prepared as outlined above, with a molecule capable of functioning both as an alkylating and an acylating agent to form a racemic mixture of aminimides; as before the use of  $\text{BrCH}_2\text{COCl}$  is shown below, but other bifunctional species, such as bromoalkyl isocyanates, 2-bromoalkyl oxazolones, etc. may also be used.

2. Reaction of the racemate from above with an asymmetrically disubstituted hydrazine to form the hydrazide:

3. Alkylation of the product from step 3 with a bifunctional molecule capable of alkylation and acylation, which may be the same as that used in step 1 or different, to form a mixture of diastereomeric aminimides.

4. Reaction of the product from step 4 with a suitable asymmetrically disubstituted hydrazine to form the hydrazide, as shown:



6. Repetition of steps 4, and 5 to build the desired aminimide polymer sequence.

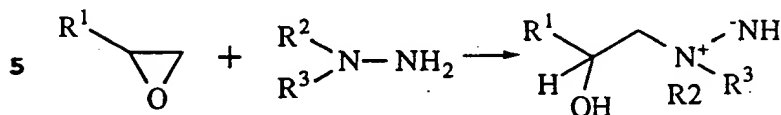
8. Capping of the sequence, if desired, using e.g. methyl bromide to produce a sequence such as shown below.



Polymerization of Aminimide Subunits Using Hydrazinolysis of an Ester in the Presence of an Epoxide

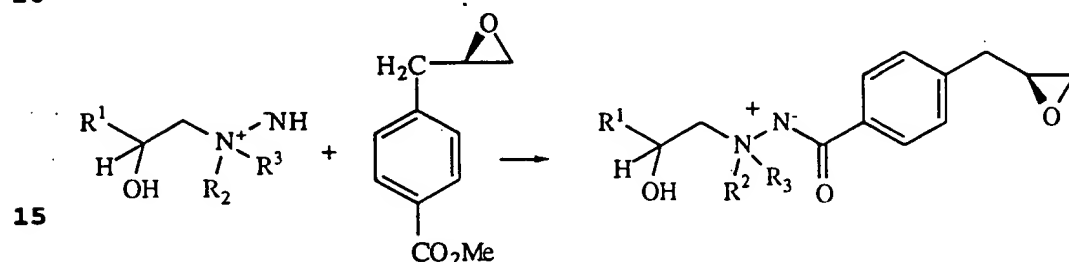
The following steps are involved in this synthesis:

1. Formation of an aminimine from the reaction of an 1,1-asymmetrically disubstituted hydrazine with an epoxide;



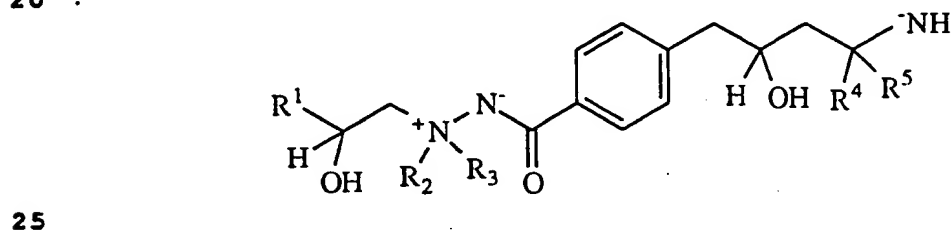
2. The aminimine is reacted with an ester-epoxide to give an aminimide;

10



3. Reaction of the aminimide with an asymmetrically disubstituted hydrazine to form an aminimide-aminimine

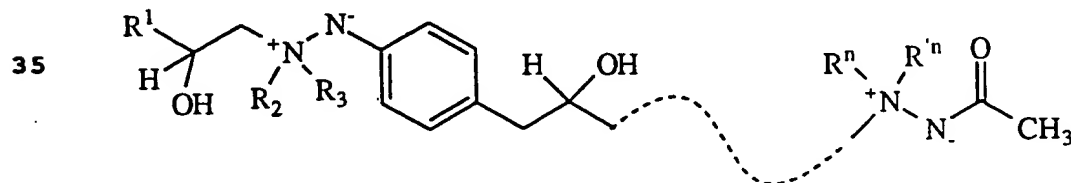
20 :



4. Repetition of steps 2 and 3 using the appropriate hydrazines and epoxy-esters in each step to produce the desired aminimide sequence.

30

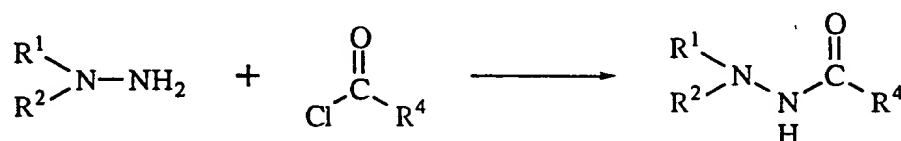
5. "Capping" of the final sequence, if desired, by acylation with a simple ester, such as methyl acetate, to produce the designed aminimide ligand shown:



Synthesis of Hydrazides

- 5 1,1-disubstituted hydrazine with an activated acyl derivative or an isocyanate, in a suitable organic solvent, e.g. methylene chloride, toluene, ether, etc. in the presence of a base such as triethylamine to neutralize the haloacid generated during the acylation.

10



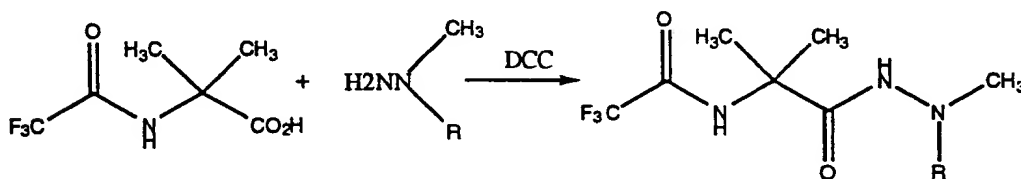
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- Activated acyl derivatives include acid chlorides, chlorocarbonates, chlorothiocarbonates, etc.; the acyl derivative may also be replaced with a suitable carboxylic acid and a condensing agent such as dicyclohexylcarbodiimide (DCC).

20

An example of the latter is the synthesis of the trifluoromethylhydrazides shown below:

25



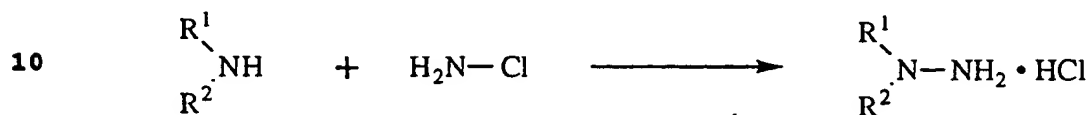
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- In this reaction a solution of 2-trifluoroacetamidoisobutyric acid in dry THF is stirred and an equivalent amount of dicyclohexylcarbodiimide is added. The reaction is subsequently stirred for three minutes, after which an equimolar quantity of the 1-substituted-1-methylhydrazine is added neat. Dicyclohexylurea precipitates immediately. The resultant suspension is stirred for one hour, filtered to remove

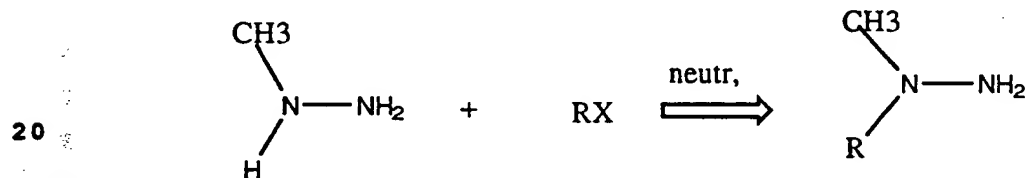
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the insoluble urea and the solvent is removed on a rotary evaporator to afford the crude hydrazide.

5 The desired 1,1-disubstituted hydrazines may be readily prepared in a number of ways well known in the art; one is the reaction of a secondary amine with  $\text{NH}_2\text{Cl}$  in an inert organic solvent.



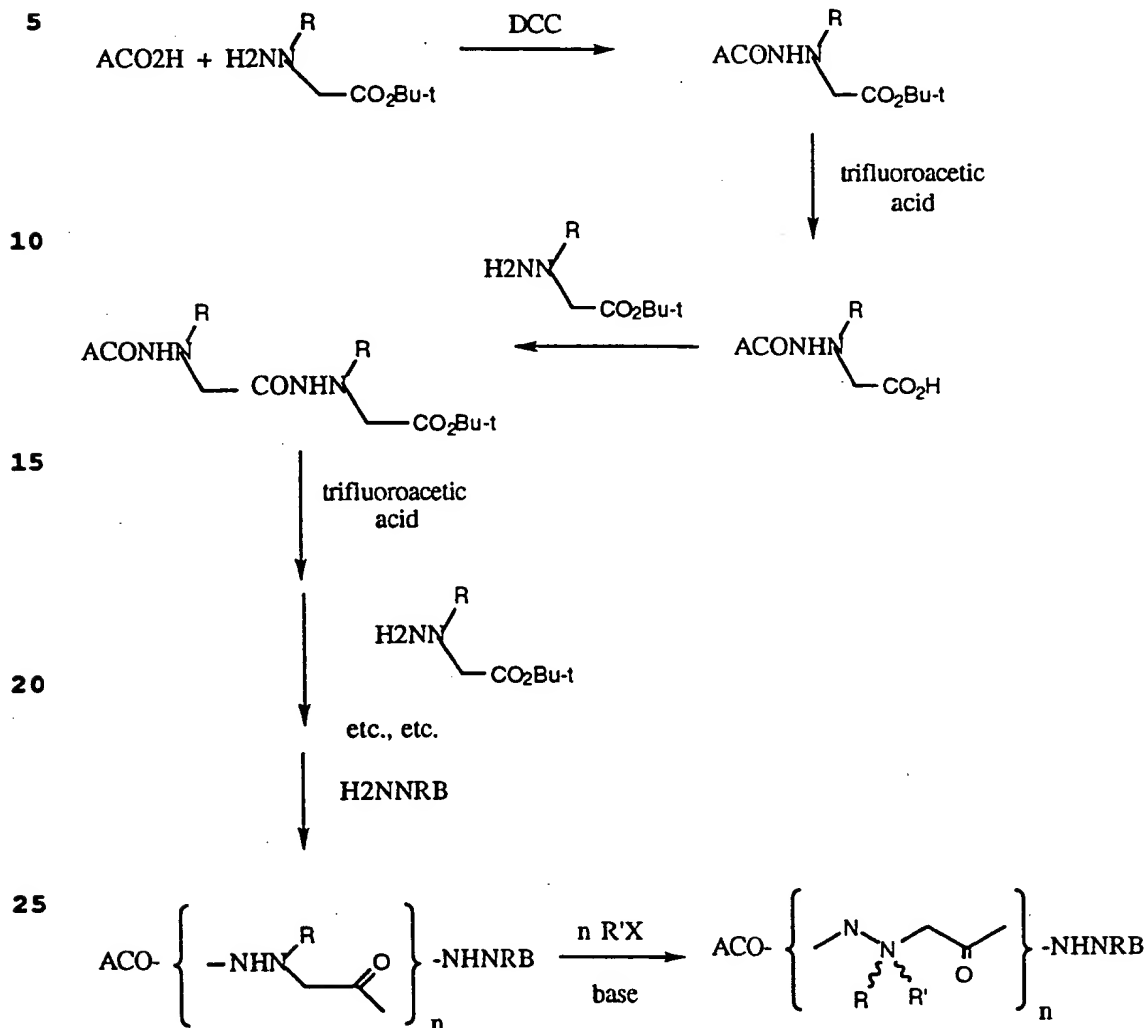
A second synthetic route for the preparation of hydrazines is alkylation of monoalkyl hydrazines, shown below for methyl  
15 hydrazine:



This reaction is carried out by reacting a solution of methylhydrazine in THF, cooled at  $0^\circ\text{C}$  with a solution of an  
25 equimolar amount of the alkyl halide in THF added dropwise with stirring over a period of 30 minutes. The reaction is stirred at  $0^\circ\text{C}$  for another 15 minutes, then heated to reflux and held at reflux for two hours. A water-cooled downward condenser is set up and approximately half of the solvent is removed by  
30 distillation. The residue is poured into water, which is then made basic by the addition of concentrated aqueous  $\text{NaOH}$ . The layers are separated, the aqueous phase is extracted with ether and the combined organic phases are washed with water, dried over  $\text{MgSO}_4$  and concentrated by distillation. Distillation at reduced  
35 pressure affords the 1-substituted-1-methylhydrazine as a colorless liquid.

Polymers Produced by Hydrazides

Polymers containing designed sequences of substituted hydrazones may be produced using the following steps:

30 Mixed Modules

All of the oxazolone, aminimide and hydrazide modules and monomers illustrated above may be mixed and matched to provide a variety of mixed-backbone polymers having specific properties, functionalities and sequences.

35

## Substituents

Any of the various R and R' groups illustrated in all of the oxazolone, aminimide and hydrazide structures may be selected from among the following list:

5

1) Amino acid derivatives of the form (AA)N, which would include, for example, natural and synthetic amino acid residues (N=1) including all of the naturally occurring alpha amino acids, especially alanine, arginine, asparagine, aspartic acid, 10 cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine; the naturally occurring disubstituted amino acids, such as amino isobutyric acid, and isovaline, etc.; a variety of synthetic amino acid residues, including 15 alpha-disubstituted variants, species with olefinic substitution at the alpha position, species having derivatives, variants or mimetics of the naturally occurring side chains; N-Substituted glycine residues; natural and synthetic species known to functionally mimic amino acid residues, such as statine, bestatin, etc. Peptides 20 (N=2-30) constructed from the amino acids listed above, such as angiotensinogen and its family of physiologically important angiotensin hydrolysis products, as well as derivatives, variants and mimetics made from various combinations and permutations of all the natural and synthetic residues listed above. Polypeptides 25 (N=31-70), such as big endothelin, pancreastatin, human growth hormone releasing factor and human pancreatic polypeptide. Proteins (N>70) including structural proteins such as collagen, functional proteins such as hemoglobin, regulatory proteins such as the dopamine and thrombin receptors.

30

2) Nucleotide derivatives of the form (NUCL)N, which includes natural and synthetic nucleotides (N=1) such as adenosine, thymine, guanine, uridine, cytosine, derivatives of these and a variety of variants and mimetics of the purine ring, the sugar ring, 35 the phosphate linkage and combinations of some or all of these. Nucleotide probes (N=2-25) and oligonucleotides (N>25) including all of the various possible homo and heterosynthetic combinations and permutations of the naturally occurring nucleotides, derivatives

and variants containing synthetic purine or pyrimidine species or mimics of these, various sugar ring mimetics, and a wide variety of alternate backbone analogues including but not limited to phosphodiester, phosphorothionate, phosphorodithionate, phosphoramidate, alkyl phosphotriester, sulfamate, 3'-thioformacetal, methylene(methylimino), 3-N-carbamate, morpholino carbamate and peptide nucleic acid analogues.

3) Carbohydrate derivatives of the form  $(CH)_n$ . This would include natural physiologically active carbohydrates such as including related compounds such as glucose, galactose, sialic acids, beta-D-glucosylamine and nojirimycin which are both inhibitors of glucosidase, pseudo sugars, such as 5a-carba-2-D-galactopyranose, which is known to inhibit the growth of *Klebsiella pneumonia* ( $n=1$ ), synthetic carbohydrate residues and derivatives of these ( $n=1$ ) and all of the complex oligomeric permutations of these as found in nature, including high mannose oligosaccharides, the known antibiotic streptomycin ( $n>1$ ).

4) A naturally occurring or synthetic organic structural motif. This term is defined as meaning an organic molecule having a specific structure that has biological activity, such as having a complementary structure to an enzyme, for instance. This term includes any of the well known base structures of pharmaceutical compounds including pharmacophores or metabolites thereof. These include beta-lactams, such as penicillin, known to inhibit bacterial cell wall biosynthesis; dibenzazepines, known to bind to CNS receptors, used as antidepressants; polyketide macrolides, known to bind to bacterial ribosomes, etc. These structural motifs are generally known to have specific desirable binding properties to ligand acceptors.

5) A reporter element such as a natural or synthetic dye or a residue capable of photographic amplification which possesses reactive groups which may be synthetically incorporated into the oxazolone structure or reaction scheme and may be attached through the groups without adversely interfering with the reporting functionality of the group. Preferred reactive groups are amino, thio, hydroxy, carboxylic acid, carboxylic acid ester,



particularly methyl ester, acid chloride, isocyanate alkyl halides, aryl halides and oxirane groups.

5 6) An organic moiety containing a polymerizable group such as a double bond or other functionalities capable of undergoing condensation polymerization or copolymerization. Suitable groups include vinyl groups, oxirane groups, carboxylic acids, acid chlorides, esters, amides, lactones and lactams. Other organic moiety such as those defined for R and R' may also be used.

10 7) A macromolecular component, such as a macromolecular surface or structures which may be attached to the oxazolone modules via the various reactive groups outlined above in a manner where the binding of the attached species to a  
15 ligand-receptor molecule is not adversely affected and the interactive activity of the attached functionality is determined or limited by the macromolecule. This includes porous and non-porous inorganic macromolecular components, such as, for example, silica, alumina, zirconia, titania and the like, as commonly  
20 used for various applications, such as normal and reverse phase chromatographic separations, water purification, pigments for paints, etc.; porous and non-porous organic macromolecular components, including synthetic components such as styrene-divinyl benzene beads, various methacrylate beads, PVA beads,  
25 and the like, commonly used for protein purification, water softening and a variety of other applications, natural components such as native and functionalized celluloses, such as, for example, agarose and chitin, sheet and hollow fiber membranes made from nylon, polyether sulfone or any of the materials mentioned above. The molecular weight of these macromolecules may range from  
30 about 1000 Daltons to as high as possible. They may take the form of nanoparticles (dp=100-1000Angstroms ), latex particles (dp=1000-5000Angstroms), porous or non-porous beads (dp=0.5-1000 microns), membranes, gels, macroscopic surfaces or  
35 functionalized or coated versions or composites of these.

8) A structural moiety selected from the group including cyano, nitro, halogen, oxygen, hydroxy, alkoxy, thio, straight or branched chain alkyl, carbocyclic aryl and substituted or

heterocyclic derivatives thereof, wherein R and R' may be different in adjacent n units and have a selected stereochemical arrangement about the carbon atom to which they are attached;

As used herein, the phrase linear chain or branched  
5 chained alkyl groups means any substituted or unsubstituted acyclic carbon-containing compounds, including alkanes, alkenes and alkynes. Alkyl groups having up to 30 carbon atoms are preferred. Examples of alkyl groups include lower alkyl, for  
10 example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl; upper alkyl, for example, cotyl, nonyl, decyl, and the like; lower alkylene, for example, ethylene, propylene, propyldiene, butylene, butyldiene; upper alkenyl such as 1-decene, 1-nonene, 2,6-dimethyl-5-octenyl, 6-ethyl-5-octenyl or heptenyl, and the like; alkynyl such as 1-ethynyl, 2-butylnyl, 1-pentylnyl and  
15 the like. The ordinary skilled artisan is familiar with numerous linear and branched alkyl groups, which are within the scope of the present invention.

In addition, such alkyl group may also contain various  
substituents in which one or more hydrogen atoms has been  
20 replaced by a functional group. Functional groups include but are not limited to hydroxyl, amino, carboxyl, amide, ester, ether, and halogen (fluorine, chlorine, bromine and iodine), to mention but a few. Specific substituted alkyl groups can be, for example, alkoxy  
such as methoxy, ethoxy, butoxy, pentoxy and the like,  
25 polyhydroxy such as 1,2-dihydroxypropyl, 1,4-dihydroxy-1-butyl , and the like; methylamino, ethylamino, dimethylamino, diethylamino, triethylamino, cyclopentylamino, benzylamino, dibenzylamino, and the like; propanoic, butanoic or pentanoic acid  
groups, and the like; formamido, acetamido, butanamido, and the  
30 like, methoxycarbonyl, ethoxycarbonyl or the like, chloroformyl, bromoformyl, 1,1-chloroethyl, bromoethyl ,and the like, or dimethyl or diethyl ether groups or the like.

As used herein, substituted and unsubstituted  
carbocyclic groups of up to about 20 carbon atoms means cyclic  
35 carbon-containing compounds, including but not limited to cyclopentyl, cyclohexyl, cycloheptyl, admantyl, and the like. such cyclic groups may also contain various substituents in which one or

more hydrogen atoms has been replaced by a functional group. Such functional groups include those described above, and lower alkyl groups as described above. The cyclic groups of the invention may further comprise a heteroatom. For example, in a  
5 specific embodiment, R<sub>2</sub> is cyclohexanol.

As used herein, substituted and unsubstituted aryl groups means a hydrocarbon ring bearing a system of conjugated double bonds, usually comprising an even number of 6 or more (pi) electrons. Examples of aryl groups include, but are not limited  
10 to, phenyl, naphthyl, anisyl, toluyl, xylenyl and the like. According to the present invention, aryl also includes aryloxy, aralkyl, aralkyloxy and heteroaryl groups, e.g., pyrimidine, morpholine, piperazine, piperidine, benzoic acid, toluene or thiophene and the like. These aryl groups may also be substituted with any number  
15 of a variety of functional groups. In addition to the functional groups described above in connection with substituted alkyl groups and carbocyclic groups, functional groups on the aryl groups can be nitro groups.

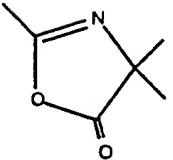
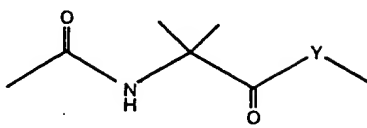
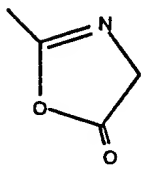
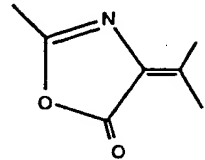
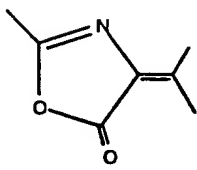
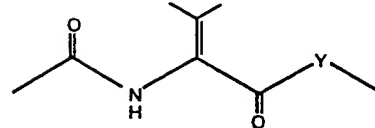
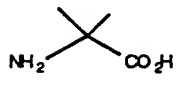
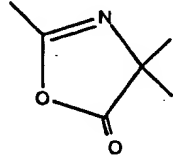
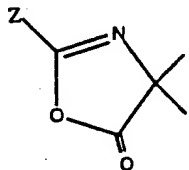
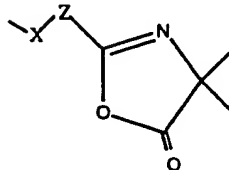

As mentioned above, these structural moieties can also  
20 be any combination of alkyl, carbocyclic or aryl groups, for example, 1-cyclohexylpropyl, benzylcyclohexylmethyl, 2-cyclohexyl-propyl, 2,2-methylcyclohexylpropyl, 2,2-methylphenylpropyl, 2,2-methylphenylbutyl, and the like.

#### 25 Reactive Groups

Specifically preferred reactive groups to generate the aminimide and oxazolone structures and the resulting base modules are listed below in tables 1, 2 and 3. The bonds in the structures in these figures represent potential points of attachment  
30 to the first and second compounds and to the base modules.

Specifically preferred reactive groups to generate the aminimide and oxazolone structures and the resulting base modules are listed below in tables 1, 2 and 3. The bonds in the structures in these figures represent potential points of attachment  
35 for the attachment of the structural diversity elements to the first and second compounds and to the base modules.

Table 1. Oxazolone Modules

	Reactivity Groups	Base Modules
5	 $\text{HY}-$ $(Y = \text{N}, \text{S}, \text{O})$	
10	 $\text{C=O}$	
15	 $\text{HY}-$ $(Y = \text{N}, \text{S}, \text{O})$	
20	 $-\text{CO}_2\text{H}/\text{Cl}$ $(\text{ClCO}_2\text{Et}/\text{Et}_3\text{N})$	
25	 $\text{HX}-$ $(X = \text{S}^-, \text{N}^-)$ $(Z = \text{CH}_2=\text{CH}-, \text{etc.})$	
30	 Represents potential points of attachment	

35

Table 2. Aminimide Modules

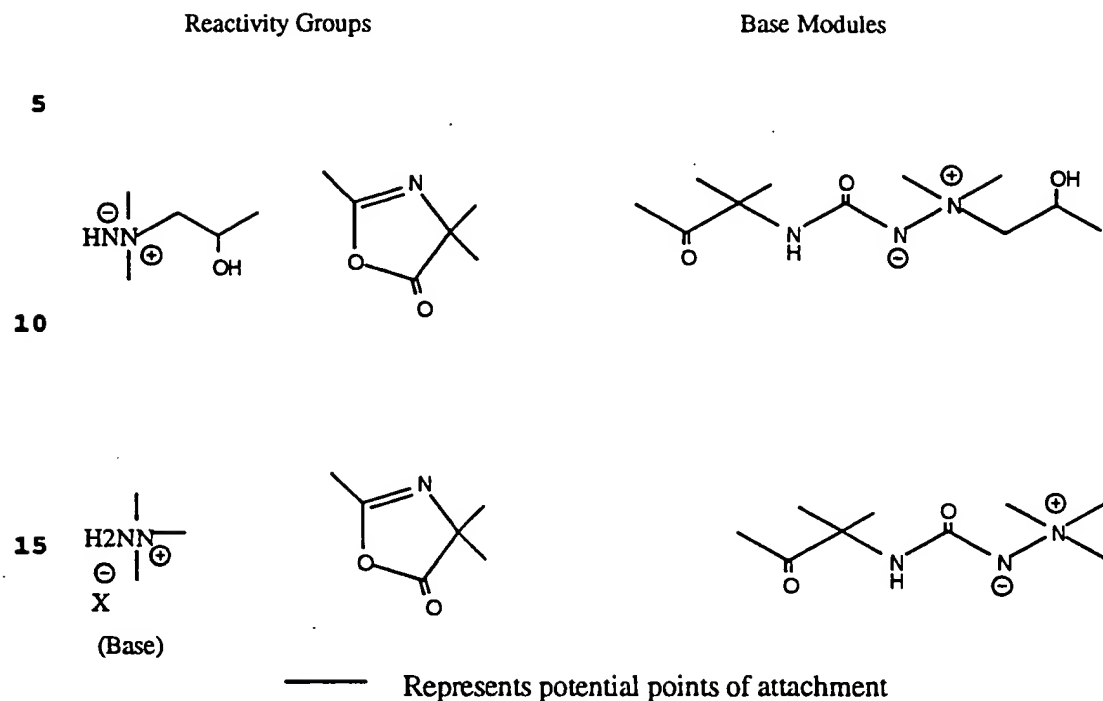
	Reactivity Groups		Base Modules
5	— COOH	$\text{H}_2\text{NN}$	— CONHN
	— NCO	$\text{H}_2\text{NN}$	— NHCONHN
	— OCOCi	$\text{H}_2\text{NN}$	— OCONHN
10	— SCOCi	$\text{H}_2\text{NN}$	— SCONHN
	— CONHN	— X (neutr.)	$\text{— CONN}^{\ominus\oplus}$
15	— CONHN		$\text{— CONN}^{\ominus\oplus}$
	— NHCONHN	— X (neutr.)	$\text{— NHCONN}^{\ominus\oplus}$
	— NHCONHN		$\text{— NHCONN}^{\ominus\oplus}$
20	— OCONHN	— X (neutr.)	$\text{— OCONN}^{\ominus\oplus}$
	— OCONHN		$\text{— OCONN}^{\ominus\oplus}$
25	— SCONHN	— X (neutr.)	$\text{— SCONN}^{\ominus\oplus}$
	— SCONHN		$\text{— SCONN}^{\ominus\oplus}$
30	— SCONHN		
35	— SCONHN		

— Represents potential points of attachment

Table 2. Continued - Aminimide Modules

	Reactivity Groups		Base Modules
5			
10			
15		BASE	
20			
25			
30			
35	— Represents potential points of attachment		

Table 3. Aminimide-Oxazolone Modules



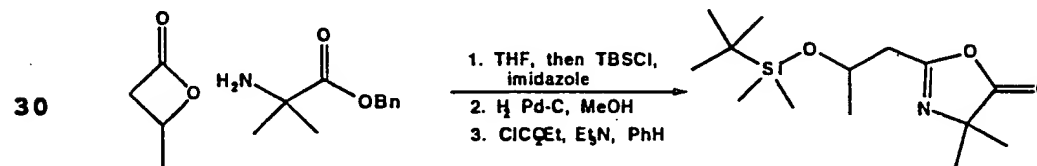
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## EXAMPLE 1.

This example describes preparation of a tetramer by alternating ring-opening/Michael-addition reactions followed by chain polymerizations.

25

## Step 1.



In the first synthetic step, a solution of  $\gamma$ -butyrolactone (8.61 g, 0.1 mole, 8.15 mL) in THF (150 mL) is cooled at 0 °C while a solution of benzyl 2-aminoisobutyrate (19.3 g, 0.1 mole) in THF (100 mL) is added. The mixture is stirred at 0 °C for two hours, then room temperature for four hours, then is treated with tert-butyldimethylsilyl chloride (15.1 g, 0.1 mole) and

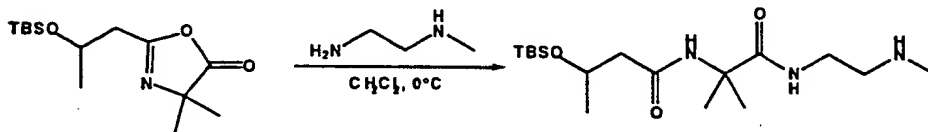
35

imidazole (13.6 g, 0.2 mole) added in alternating portions as the solids. The mixture is stirred overnight at room temperature, the solids are removed by filtration, and the filtrate is concentrated in vacuo. The residue is dissolved in methanol (100 mL), palladium on carbon catalyst (5 % Pd, 500 mg) is added, and the solution stirred under an atmosphere of hydrogen gas until the ester is exhausted (reaction is monitored in progress by volume of absorbed H<sub>2</sub> gas and by TLC). Following complete removal of the benzylic

functionality, the catalyst is removed by filtration with the aid of celite. The precipitate is washed with methanol (3 x 100 mL) and the combined filtrates are concentrated in vacuo. The residue is crystallized, then recrystallized from ethyl acetate to afford the protected acid (21.7 g, 0.072 mole, 72 %).

This acid is dissolved in ethyl acetate (300 mL) and cooled at 0 °C while ethyl chloroformate (7.77 g, 0.072 mole, 6.85 mL) is added, followed by triethylamine (7.25 g, 0.072 mole, 9.98 mL). After cessation of gas evolution (ca. four hours), the triethylamine hydrochloride is removed by filtration and the filtrate is concentrate to afford crude 2-(2-tert-butyldimethylsilyloxy propyl)-4,4-dimethyl-5-oxazolone as a yellow oil (23.4 g). Recrystallization from ethyl acetate affords the pure product (13.7 g, 67 %, 0.048 mole). The material gave satisfactory spectral data (300 MHz NMR proton signals corresponding to silyl group butyl : silyl group methyls : oxazolone gem-dimethyl integrals 9:6:6; IR 1820 cm<sup>-1</sup> azlactone band).

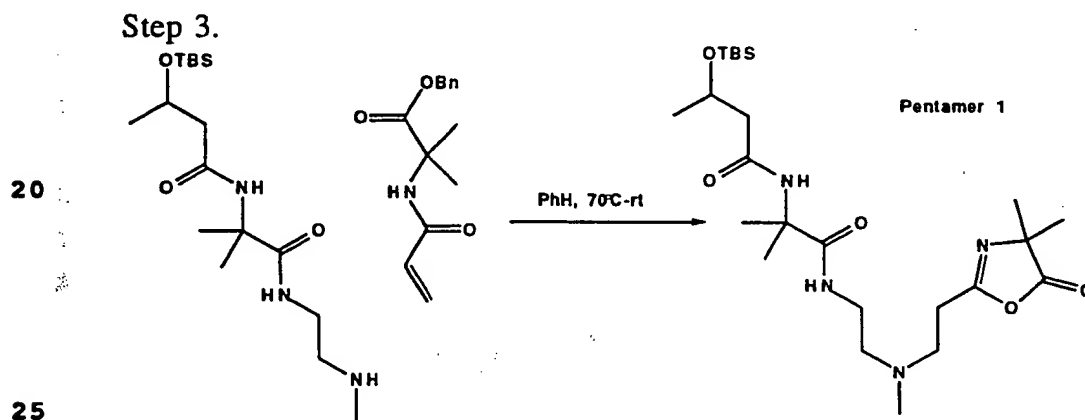
### Step 2.



A solution of of 95% N-methylethylenediamine (3.56 g, 48 mmol, 4.23 mL) in methylene chloride (75 mL) is cooled in an ice bath while a solution of 2-(2-tert-butyldimethylsilyloxy propyl)-4,4-dimethyl-5-oxazolone (13.7



g, 48 mmol) in methylene chloride (100 mL) is added such that the temperature remains below 5 °C. The solution is stirred at room temperature for 15 minutes while a white precipitate forms. The mixture is stirred for an additional 2 h at 0 °C. The solids are removed by filtration and washed with methylene chloride (25 mL) and air dried to yield the ring-opened adduct (12.87 g, 36 mmol, 75%), identified by nuclear magnetic resonance (NMR) and Fourier transform infrared (FTIR) spectroscopy as follows: NMR (CDCl<sub>3</sub>): CH<sub>3</sub>-N/gem (CH<sub>3</sub>)<sub>2</sub> ratio 1:2; tert-butyldimethylsilyl - splitting pattern in 0-1 ppm region, integration ratios and D<sub>2</sub>O exchange experiments diagnostic for structure. FTIR (nujol mull): azlactone CO band at 1820 cm<sup>-1</sup> absent; strong amide bands present in 1670 - 1700 cm<sup>-1</sup> region.



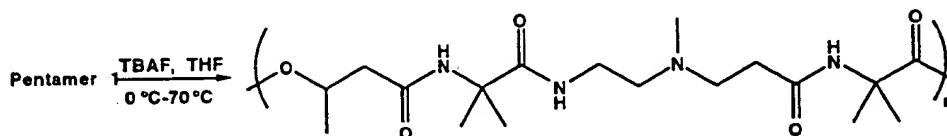
A solution of of the ring-opened adduct (8.98 g, 25 mmol) and 4,4-dimethyl-2-vinylazlactone ( 3.48 g, 25 mmol) in benzene (50 mL) is heated to 70 °C for 4 hours. The flask is cooled to room temperature and allowed to stand under an inert atmosphere for 3 days. The solvent is decanted off from the thick oil that forms. This oil is dissolved in acetone (ca 50 mL) and concentrated to produce another thick oil, which is concentrated under vacuum at 1 torr overnight to yield 9.34 g of a white crystalline solid (25 mmol), identified by NMR and FTIR spectroscopy as 2-(N-(2-(2-(3-tert-butyldimethylsilyloxy butyramido)-isobutyramido)-ethyl)-N-methyl-2-aminoethyl)-4,4-dimethyl-5-oxazolone: NMR: CH<sub>3</sub>-N/gem (CH<sub>3</sub>)<sub>2</sub> ratio 1:4; tert-

butyldimethylsilyl - splitting pattern in 0-1 ppm region,  
integration ratios and D<sub>2</sub>O exchange experiments diagnostic for  
structure. FTIR (nujol mull): strong azlactone CO band at 1820 cm<sup>-1</sup>.

5

### Construction of the Poly(pentamer)

10



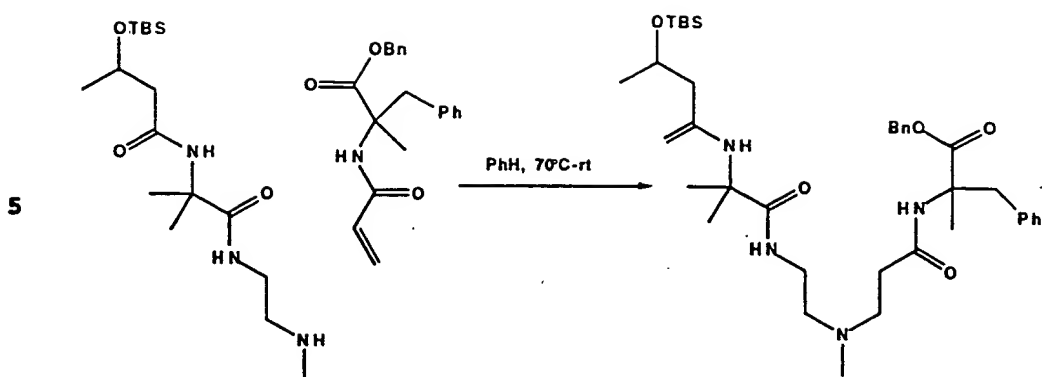
Polymerization of the mono(pentamer) -This material is  
15 dissolved in THF (500 mL) and cooled at 0 °C while a solution of  
tetra-*n*-butylammonium fluoride (1.0M in THF, 25 mL, 25 mmol) is  
added. The exotherm is controlled by the rate of addition of the  
fluoride reagent. The mixture is then heated briefly to 70 °C and  
20 cooled to room temperature. Water (100 mL) is added and the  
layers are stirred, then separated. The organic phase is dried  
(sat'd aq NaCl, MgSO<sub>4</sub>), and concentrated in vacuo (18 torr, then  
0.1 torr 10 hours) to afford the polymer (9.60 g). This material  
showed no signals for the tert-butyldimethylsilyl group in the  
25 proton NMR spectrum and the azlactone band was absent in the  
infrared spectrum.

### EXAMPLE 2.

This example illustrates the preparation of a tris(pentameric)  
30 module and its assembly into a polymer.

Step 1.

35

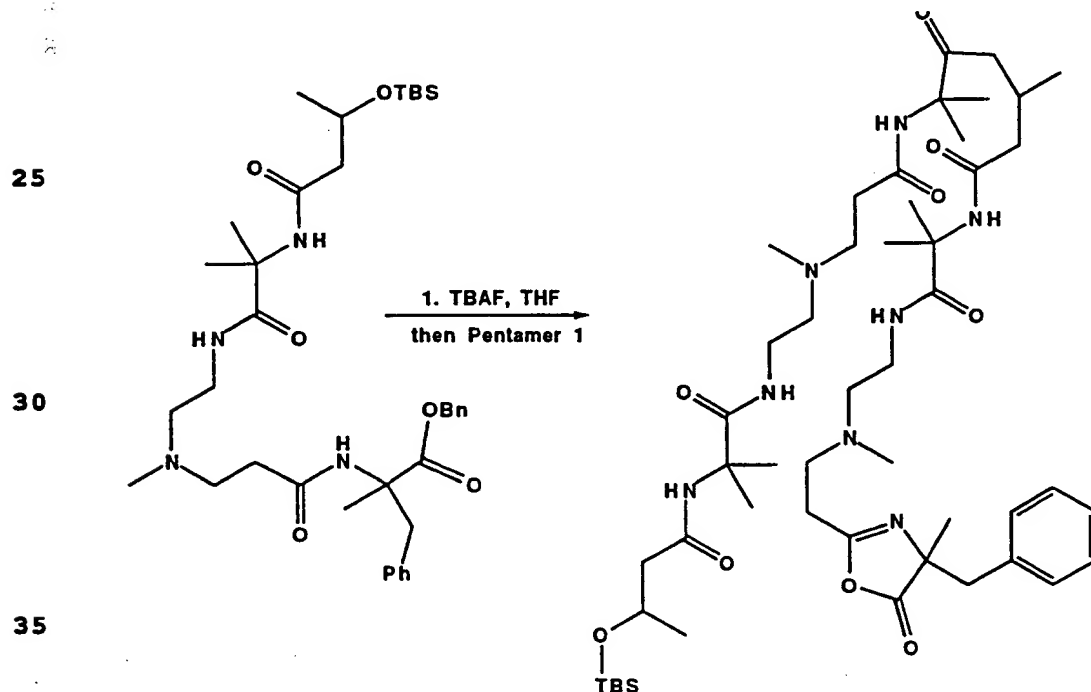


10

A solution of the ring-opened adduct (8.98 g, 25 mmol) and benzyl 3-phenyl-2-methyl-2-acrylamidopropionate (8.03 g, 25 mmol) in benzene (50 mL) is heated to 70 °C for 4 hours. The flask is cooled to room temperature and allowed to stand under an inert atmosphere for 3 days. The solvent is decanted off from the thick oil that forms. The residue is crystallized, then recrystallized from ethyl acetate. to afford the protected benzyl ester adduct (15.34 g, 23 mmol, 90%)

15

20 Step 2.



The product is dissolved in THF (250 mL) and a solution of TBAF (1.0M, 23 mmol, 23 mL) is added and the reaction stirred for one hour at room temperature, then cooled at 0 °C while a solution of 2-(N-(2-(2-(3-tert-butyldimethylsilyloxy butyramido)-isobutyramido)-ethyl)-N-methyl-2-aminoethyl)-4,4-dimethyl-5-oxazolone (11.45 g, 23 mmol) in THF (150 mL) is added with stirring. The reaction is stirred overnight at room temperature, then partitioned between water (200 mL) and THF. The aqueous phase is separated and extracted with ether (2 x 200 mL) and the combined organics are dried (sat'd aq NaCl, MgSO<sub>4</sub>) and concentrated to afford a solid (22.0 g).

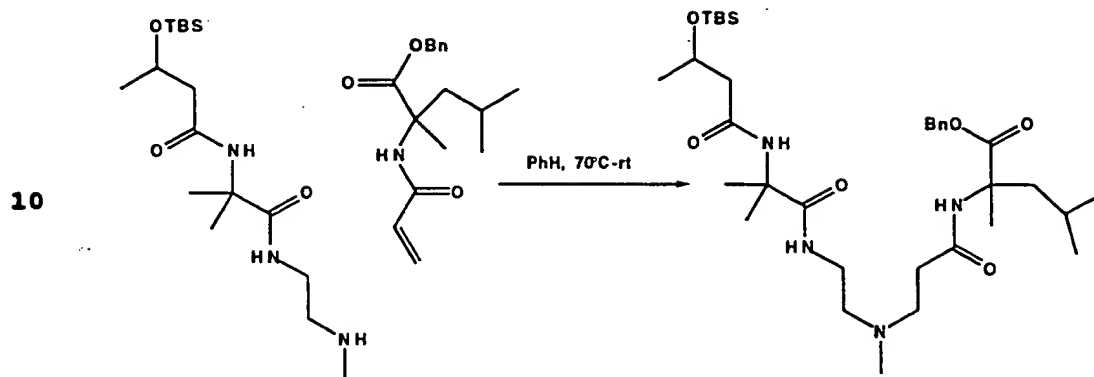
A suspension of this solid and palladium on carbon catalyst (5 % Pd, 500 mg) in methanol (200 mL) is stirred under an atmosphere of hydrogen gas until the ester is exhausted (reaction is monitored in progress by volume of absorbed H<sub>2</sub> gas and by TLC). Following complete removal of the benzylic functionality, the catalyst is removed by filtration with the aid of celite. The filter pad is washed with methanol (3 x 100 mL) and the combined filtrates are concentrated in vacuo to afford a viscous syrup that is used directly.

This acid is dissolved in ethyl acetate (100 mL) and cooled at 0 °C while ethyl chloroformate (2.32 g, 23 mmol, 2.04 mL) is added, followed by triethylamine (2.16 g, 23 mmol, 2.98 mL). After cessation of gas evolution (approximately two hours), the triethylamine hydrochloride is removed by filtration and the filtrate is concentrated to afford the crude product as a yellow oil (23.4 g). A pure sample of this product is obtained Purified by chromatographic purification on RP-C<sub>18</sub> silica gel (methanol-water gradient elution) to give 2-(N-(2-(3-(2-(N-(2-(2-(3-tert-butyldimethyl silyloxybutyramido)-isobutyramido)-ethyl)-N-methyl-3-propanamido)-isobutyroxy)-butyramido)-isobutyramido)-ethyl-N-methyl-2-aminoethyl)-ethyl-4,4-dimethyl-5-oxazolone (11.43 g, 61%, 14 mmol) as an amorphous powder. The material gave satisfactory spectral data (300 MHz NMR proton signals corresponding to silyl group butyl : silyl group methyls :

oxazolone gem-dimethyl integrals 9:6:6; IR 1820 cm<sup>-1</sup> (azlactone band).

Step 3.

5



15

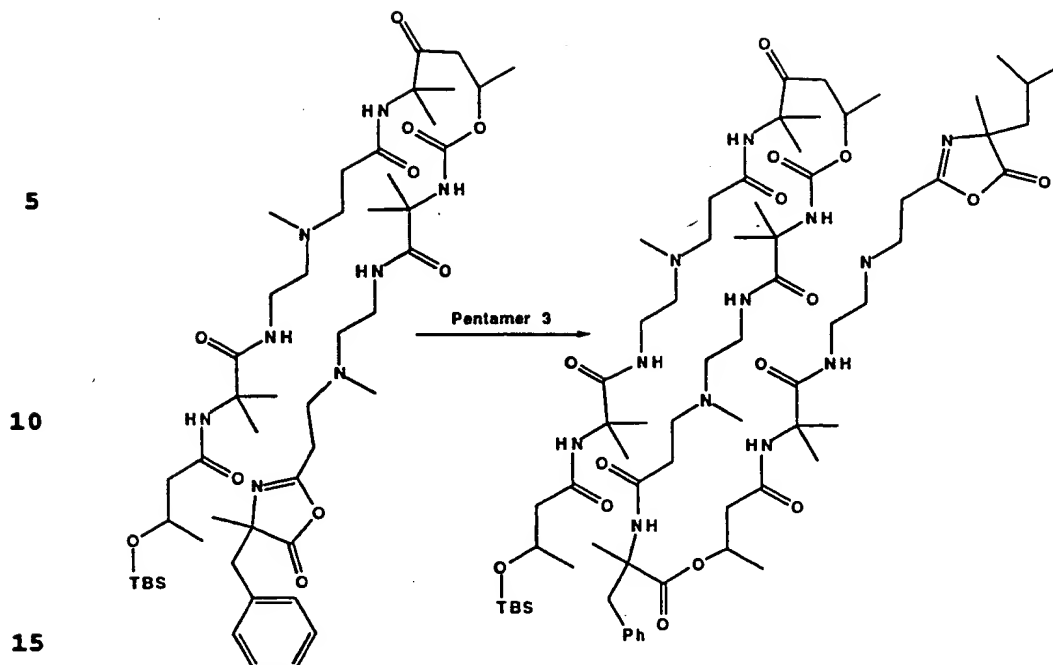
A solution of the ring-opened adduct (8.98 g, 25 mmol) and benzyl 2,4-dimethyl-2-acrylamidopentanoate (7.18 g, 25 mmol) in benzene (50 mL) is heated to 70 °C for 4 hours. The flask is cooled to room temperature and allowed to stand under an inert atmosphere for 3 days. The solvent is decanted off from the thick oil that forms. The residue is crystallized, then recrystallized from ethyl acetate to afford the protected benzyl ester adduct (13.41 g, 21 mmol, 83%)

20

25 Step 4.

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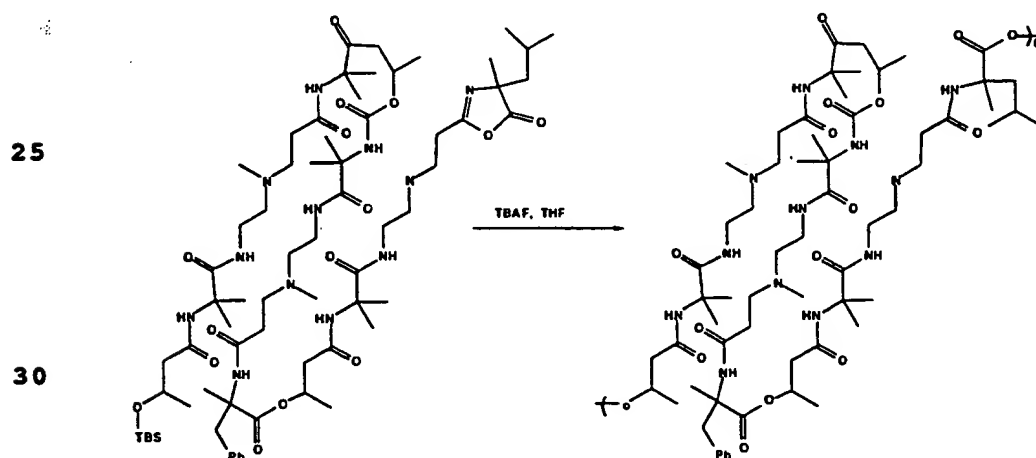
A solution of this product (8.94 g, 14 mmol) in THF (250 mL) and a solution of TBAF (1.0M, 14 mmol, 14 mL) is added and the reaction stirred for one hour at room temperature, then cooled at 0 °C while a solution of the previously prepared di-pentamer oxazolone (11.43 g, 14 mmol) in THF (150 mL) is added with stirring. The reaction is stirred overnight at room temperature, then partitioned between water (200 mL) and THF. The aqueous phase is separated and extracted with ether (2 x 200 mL) and the combined organics are dried (sat'd aq NaCl, MgSO<sub>4</sub>) and concentrated to afford a solid (22.0 g).

A suspension of this solid and palladium on carbon catalyst (5 % Pd, 250 mg) in methanol (200 mL) is stirred under an atmosphere of hydrogen gas until the ester is exhausted (reaction is monitored in progress by volume of absorbed H<sub>2</sub> gas and by TLC). Following complete removal of the benzylic functionality, the catalyst is removed by filtration with the aid of celite. The filter pad is washed with methanol (3 x 100 mL) and the combined filtrates are concentrated in vacuo to afford a viscous syrup that is used directly.

This acid is dissolved in ethyl acetate (100 mL) and cooled at 0 °C while ethyl chloroformate (1.41 g, 14 mmol, 1.24

mL) is added, followed by triethylamine (1.31 g, 14 mmol, 1.81 mL). After ten hours, the triethylamine hydrochloride is removed by filtration and the filtrate is concentrated to afford the crude product as a tan solid (23.4 g). Purification by  
 5 column chromatography on RP-C<sub>18</sub> silica gel (methanol-water gradient elution), pooling of the appropriate fractions and concentration in vacuo affords pure 2-(3-(N-(2-(2-(2-(3-(N-(2-(3-(2-(N-(2-(2-(3-tert-butyldimethylsilyloxybutyramido)-isobutyramido)-ethyl)-N-methyl-2-aminoethyl)-  
 10 propanoylamido)-isobutyroxy)-butyramido)-isobutyramido)-ethyl)-N-methyl-2-aminoethyl)-propanoylamido)-isobutyroxy)-propanoylamido)-isobutyramido)-N-methyl-ethylamino)-ethyl)-4-isobutyl-4-methyl-5-oxazolone z(3.72 g, 22%, 3 mmol) as an amorphous powder. The material gave  
 15 satisfactory spectral data (300 MHz NMR proton signals corresponding to silyl group butyl : silyl group methyls : oxazolone gem-dimethyl integrals 9:6:6; IR 1820 cm<sup>-1</sup> azlactone band).

## 20 Construction of the Polytris(pentamer)



35 Polymerization of the tris(pentamer) -This material is dissolved in THF (200 mL) and cooled at 0 °C while a solution of tetra-*n*-butylammonium fluoride (1.0M in THF, 3 mL, 3 mmol) is added. The exotherm is controlled by the rate of addition of the fluoride reagent. The mixture is then heated briefly to 70 °C and

cooled to room temperature. Water (100 mL) is added and the layers are stirred, then separated. The organic phase is dried (sat'd aq NaCl, MgSO<sub>4</sub>), and concentrated in vacuo (18 torr, then 0.1 torr 10 hours) to afford the polymer (3.38 g). This material  
5 showed no signals for the tert-butyldimethylsilyl group in the proton NMR spectrum and the azlactone band was absent in the infrared spectrum.

Further details on the reaction possibilities for the  
10 oxazolone and aminimide compounds can be found in two PCT applications PCT/US93/0--- and PCT/US93/0---, each filed on December 28, 1993, and entitled Modular Design And Synthesis of Aminimide-Derived Molecules, respectively. The content of  
15 each of those applications is expressly incorporated herein by reference thereto to the extent necessary to understand the metes and bounds of this invention.

20

25

30

35



THE CLAIMS

What is claimed is:

5           1.     A method of making a polymer having specific  
physiochemical properties which comprises:

          forming a first module having a structure which includes at least two  
structural diversity elements suitable to impart a desired physical property to  
10       a polymer which is made from said monomer; and

          reacting one or more modules to form a polymer having specific  
physiochemical properties.

15          2.     A method according to claim 1 which further comprises  
forming the base module from an aminimide compound, an oxazolone  
compound or derivatives thereof.

20          3.     A method according to claim 1 which further comprises  
forming the base module by reacting a first compound having at least one  
structural diversity element and a first reactive group, with a second  
compound having at least one structural diversity element and a second  
reactive group, wherein the first and second groups combine by an addition  
reaction.

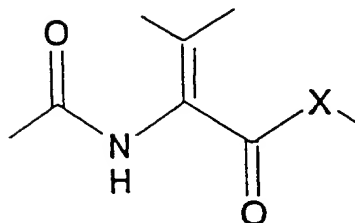
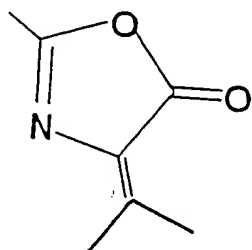
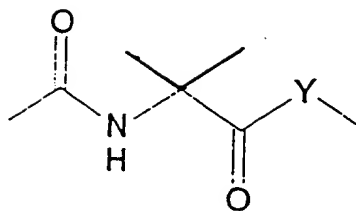
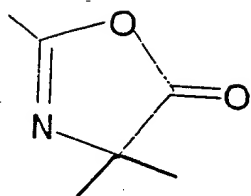
25          4.     The method according to claim 3 which further comprises  
producing the first compound by forming an oxazolone compound having at  
least one structural diversity element attached thereto.

30          5.     The method according to claim 4 which further comprises  
providing the second compound as a nucleophile or carbonyl compound  
which is capable of reaction with the oxazolone contains and which contains  
at least one structural diversity element.

35          6.     The method according to claim 5 which further comprises  
combining the first and second compounds to form a base module having  
one of the following structures:

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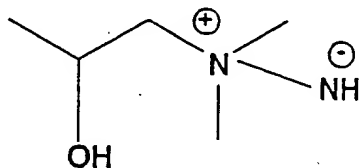


wherein at least two of the unconnected lines are connected to structural diversity elements.

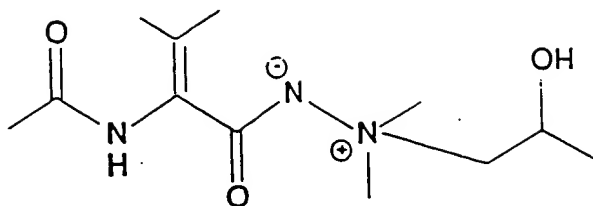
7. The method according to claim 3 which further comprises providing the first compound as an aminide-forming compound having at least one structural diversity element attached thereto.

8. The method according to claim 7 which further comprises providing the second compound as an oxazolone or ether compound which is capable of reaction with the aminide-forming compound and which contains at least one structural diversity element.

9. The method according to claim 8 which further comprises combining the first and second compounds to form a base module having one of the following structures:



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wherein at least two of the unconnected lines are connected to structural diversity elements.

10. The method of claim 9 which further comprises selecting the first and second structural diversity elements to be one of the following:

an amino acid derivative of the form  $(AA)_n$ ;

a nucleotide derivative of the form  $(NUCL)_n$ ;

a carbohydrate derivative of the form  $(CH)_n$ ;

an organic moiety of an alkyl, cycloalkyl, aryl, aralkyl or alkaryl group or a substituted or heterocyclic derivative thereof, or of a naturally occurring or synthetic organic structural motif, optionally containing a reporter element, an electrophilic group, a nucleophilic group or a polymerizable group; or

a macromolecular component.

11. The method according to claim 3 which further comprises providing at least one of the first and second compounds with at least two structural diversity elements.

12. The method according to claim 1 which further comprises providing each of the first and second compounds with at least two structural diversity elements.

13. A method according to claim 1 which further comprises sequentially reacting modules to form the polymer.

14. A method according to claim 1 which further comprises reacting a plurality of the same modules to form the polymer.

15. A method according to claim 1 which further comprises reacting a plurality of different modules to form the polymer.

5 16. A method according to claim 1 which further comprises selecting the module to be a derivative or mimic of a peptide, protein, oligonucleotide, oligosaccharide, carbohydrate, pharmaceutical or pharmacophore.

10 17. A method according to making a polymer having a desired water solubility which comprises:

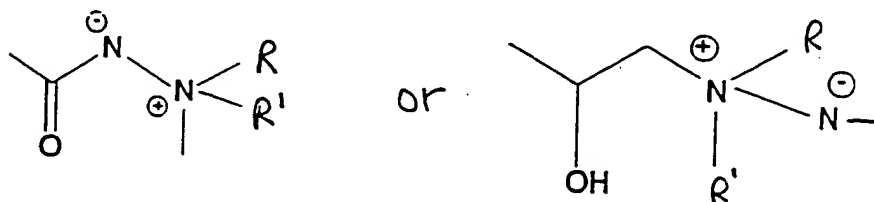
forming a first base module having a having a hydrophobic moiety attached thereto;

15 forming a second base module having a having a hydrophilic moiety attached thereto; and

reacting one or more of the first and second base modules to form a polymer having a specific molecular weight, a specific length and a particular water solubility.

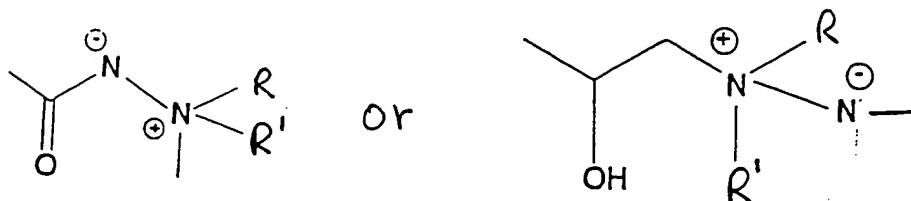
20 18. A method according to claim 17 which further comprises sequentially reacting said modules to control the addition of each modules to the polymer.

25 19. A method according to claim 17 which further comprises: selecting a first base module having the formula



wherein R and R' are the same or different and are alkyl, carboxylic, aryl or an organic moiety exhibiting hydrophobicity;

selecting a second base module having the formula



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wherein R and R' are the same or different and are alkyl, carbocyclic, aryl or an organic moiety exhibiting hydrophilicity;

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polymerizing said modules in a manner which is effective to control the addition of each module to a developing polymer chain until a polymer having the desired water solubility is produced.

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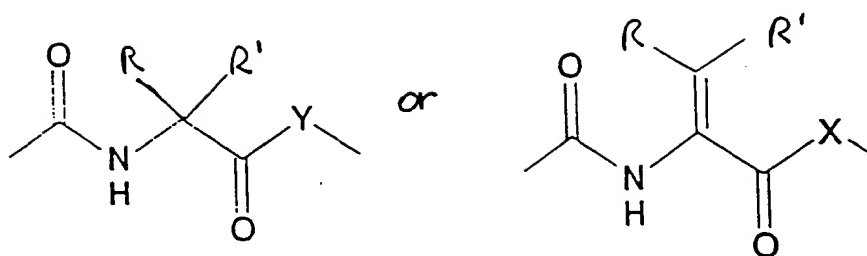
20. A method according to claim 19 wherein R and R' of the first base module are selected from the group of hydrophobic moieties consisting of long chain alkyl groups.

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21. A method according to claim 19 wherein R and R' of the second base module are selected from the group of hydrophilic moieties comprising alkyl, carbocyclic and aryl groups that also contain carboxylic acid groups.

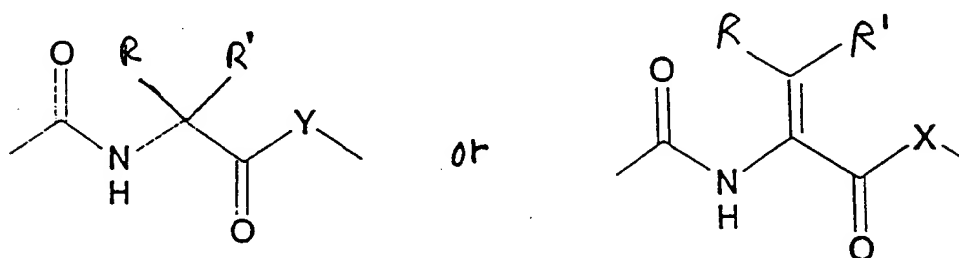
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22. A method according to claim 17 which further comprises: selecting a first base module having the formula



10 wherein R and R' are the same or different and are alkyl, carboxylic, aryl or an organic moiety exhibiting hydrophobicity;

selecting a second base module having the formula



20 wherein R and R' are the same or different and are alkyl, carbocyclic, aryl or an organic moiety exhibiting hydrophilicity;

25 polymerizing said modules in a manner which is effective to control the addition of each module to a developing polymer chain until a polymer having the desired water solubility is produced.

30 23. A method according to claim 22 wherein R and R' of the first base module are selected from the group of hydrophobic moieties consisting of long chain alkyl groups.

35 24. A method according to claim 22 wherein R and R' of the second base module are selected from the group of hydrophilic moieties comprising alkyl, carbocyclic and aryl groups that also contain carboxylic acid groups.

25. A polymer comprising at least three connected modules wherein at least one module has a structure which includes at least two structural diversity elements.

5 26. A polymer according to claim 25 wherein each module has a structure which includes at least two structural diversity elements.

27. A polymer according to claim 25 wherein the first and last modules have less than two structural diversity elements.

10 28. A polymer made according to the method of claim 17.

29. A polymer made according to the method of claim 19.

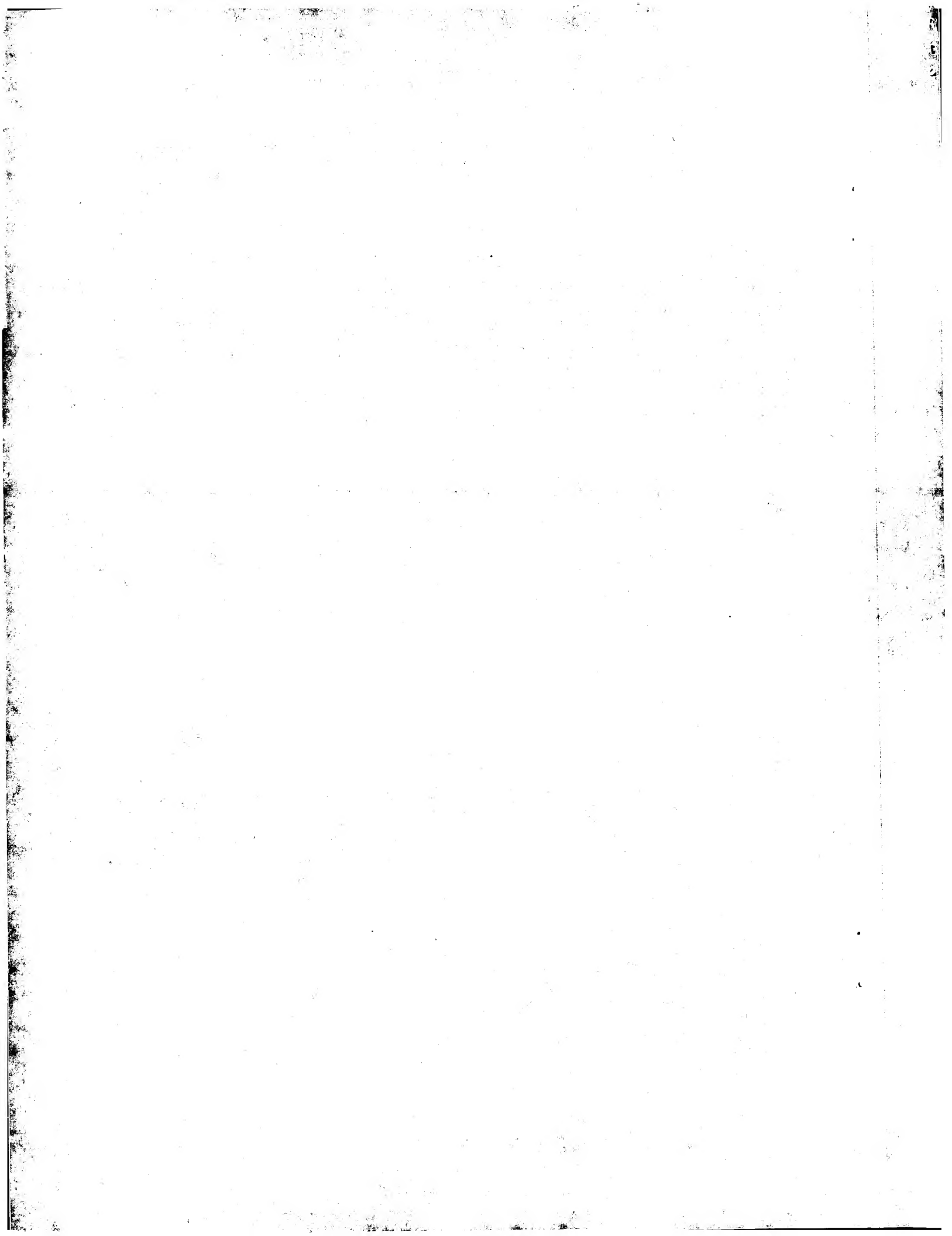
15 30. A polymer made according to the method of claim 22.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/00222

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A61K 37/00

US CL :514/12

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12; 530/323, 324, 333

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online, APS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,039,813 (FAZIO ET AL) 13 August 1991, see entire document.	1-30
A	US, A, 4,612,388 (MITA ET AL) 16 September 1986, see entire document.	1-30
A	US, A, 5,219,731 (SIH) 15 June 1993, see entire document.	1-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

20 JUNE 1994

Date of mailing of the international search report

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